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Fresh fungal challenges and novel solutions for immunocompromised patients

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Tropical fungal pathogens acquired during exotic holidays, monoclonal antibody therapy as a growing risk factor for invasive fungal disease (IFD), and novel ways of optimising antifungal prophylaxis and diagnosis-driven fungal therapy were among the hot topics in a dawn-to-dusk programme for over 300 delegates who celebrated the 30th anniversary of the International Immunocompromised Host Society (ICHS) in Budapest.

IFI risk for immunocompromised travellers

Look out for unusual fungal pathogens in immunocompromised patients who present with signs and symptoms of infection after holidaying or living in the tropics, advised Olivier Lortholary, from the Necker Enfants Malades University Hospital and Institut Pasteur, Paris, France.

As well as HIV, chronic obstructive pulmonary disease (COPD) and transplant patients, and children with primary immunodeficiency disorders, growing numbers of people receiving biotherapies, and those with diabetes, and the elderly are potential targets for fungal pathogens when travelling in Africa, South America and South East Asia.

Professor Lortholary pointed out that the spectrum of fungi to which patients may be exposed in the tropics includes dimorphic fungi such as *Histoplasma capsulatum* var *capsulatum* and, more rarely, *duboisii*, *Coccidioides immitis* or *posadasii*, and *Penicillium marneffeii*. Even outside the tropics, patients are increasingly at risk of unusual IFD, such as blastomycosis and *Cryptococcus* infection, which may go unrecognised unless patients are questioned about their recent travels.

Professor Lortholary described the case of a male patient with diabetes who returned from a holiday in Canada with a dry cough, chest pain and fever. Bronchoalveolar lavage (BAL) was initially negative but a computed tomography (CT) guided biopsy after three weeks showed blastomycosis. Professor Lortholary explained that 50-75% of cases yield positive respiratory cultures within five weeks, and he reported newly published data on 59 cases of blastomycosis in Indiana which showed that 22% of patients had diabetes, 7% COPD and 45% another underlying condition¹.

Professor Lortholary also reported the case of a single lung transplant patient whose donor turned out to have travelled in an endemic area and contracted *C. immitis*. The patient experienced a period of acute rejection and was treated for suspected invasive aspergillosis (IA) with itraconazole – something which may have delayed the true diagnosis.

Professor Lortholary concluded that immunocompromised patients should be advised to have a medical consultation before travelling to the tropics, so they can understand the risks, discuss whether their dose and duration of immunosuppressive treatment should be changed and, in the case of HIV patients, check their CD4 count. They should also be advised to report any exposure to possible fungal infection, for example, through unusual weather conditions or from building sites, while abroad.

IFD after monoclonal antibody therapy

IFD is a growing threat to patients on monoclonal antibody (MAb) therapy for rheumatoid arthritis and other autoimmune diseases, but differences in MAb characteristics, dosing and treatment duration can affect when infections are most likely to occur.

Serious infection rates of around 6% have been linked to MAb therapy. But, as Professor Thomas Patterson, from the University of Texas Health Science Center, San Antonio, Texas, USA, explained, evidence of IFD linked to biological treatments is largely based on isolated cases and small series of heterogeneous groups of patients, often with unconfirmed diagnoses and taking concomitant immunosuppressants.

The largest amount of data relates to the TNF α inhibitors, etanercept, infliximab and rituximab, as these are by far the most commonly used of the more than 25 biological therapies now approved by national licensing bodies.

In a review of 281 cases of IFD identified in a literature search of TNF α inhibitors, 80% were associated with infliximab, 16% with etanercept, and 4% with adalimumab. Fungal infections associated with infliximab occurred a median of 55 days after initiation of therapy while those associated with etanercept occurred a median of 144 days after initiation of therapy². Histoplasmosis was the most common IFD (30%), followed by candidiasis (23%), and aspergillosis (23%). Of the 90 cases for which outcome information was available, 29 deaths (32%) were recorded.

Professor Patterson concluded that physicians need to be aware of the increased risk of IFD in patients undergoing MAb therapy, so that they can pursue rapid diagnosis and aggressive antifungal therapy in order to optimise the likelihood of a successful outcome.

Role of diagnosis-driven IFD treatment becomes clearer

Diagnosis-driven treatment of IFD can reduce over-treatment with antifungal drugs associated with empirical therapy, without increasing mortality, but much depends on the availability of non-mycological diagnostic facilities, and whether patients have received mould-active prophylactic therapy. This was how Dr Johan Maertens, from the University Hospitals of Leuven, Leuven, Belgium, summed up the latest evidence to support a range of antifungal treatment strategies based on early diagnosis, using clinical features, polymerase chain reaction (PCR), galactomannan (GM) testing or CT scans.

Dr Maertens demonstrated how clinical features, notably severe sepsis/shock, lung, CNS, abdominal, skin or sinus symptoms, have been used successfully to “target” empirical therapy at patients who most need it, without increasing the infection rate or mortality in those who remain untreated³.

He also showed that PCR-based antifungal therapy in allogeneic haematopoietic stem cell transplant (HSCT) patients receiving fluconazole prophylaxis has been associated with reduced 30 day mortality compared to empirical therapy, though more – rather than fewer – patients received treatment in the PCR group than the empirical group (57% vs 36.7% respectively)⁴.

In contrast, high resolution CT (HRCT)-guided antifungal therapy has been shown to reduce antifungal usage in the early period following allogeneic transplant, in patients with antibiotic-resistant neutropenic fever for more than 72 hours, without adverse effects on IFD cases or mortality⁵.

In an open label feasibility study, discussed by Dr Maertens, an intensive diagnostic work-up (GM for 3 days, chest CT and other examinations as indicated) was used to identify patients with clinical signs of IFD who were most in need of antifungal treatment⁶. The diagnosis-driven strategy resulted in a 43% reduction in antifungal treatments compared with a standard empirical approach. At 3-month follow-up, 63% of patients with IFD survived, and no undetected IFDs were found.

Practical tips from Meet-the-Expert Sessions

Immunocompromised patients who have experienced long periods of neutropenia should probably get antifungal prophylaxis – or at least an intensive work up – even if their diagnosis doesn't fully meet guideline criteria, advised Professor Dimitrios Kontoyiannis, from MD Anderson Cancer Center, Houston, USA. He pointed out that, while guidelines recommend prophylaxis for acute myelogenous leukaemia and myelodysplastic syndrome, cumulative neutropenia and cumulative steroid use should also be used to assess need for prophylaxis in other immunosuppressed groups.

In patients with pulmonary symptoms, a negative chest CT doesn't automatically mean there is no fungal infection, warned Professor Kontoyiannis. Lesions under 1mm may not show up, so it is important to take a second scan after seven days, and to look for non-classical signs, especially in neutropenic and AML patients.

Professor Thomas Patterson explained that it is unclear what a positive GM test in the absence of measurable disease on CT really means, but combining GM with BAL increases detection by 20-30%, with advantages even in patients who have had prophylaxis. He stressed the importance of good communication between laboratory, radiologist and pulmonologist to optimise IFD detection.

Professor Kontoyiannis recommended iv voriconazole 6mg/kg as the starting treatment for Aspergillus infection, reducing to 4mg/kg, before converting to oral treatment, though Professor Patterson recommended therapeutic dose monitoring (TDM) as he had found a significant proportion of patients failed to achieve therapeutic levels, even with weight-based treatment. He added that, while patients may achieve therapeutic levels in hospital, these may drop off when they get home, possibly because improved hepatic function during recovery results in better voriconazole metabolism – something which can be predicted by results of liver function tests.

Improved HSCT practices and anti-infection strategies are paying off

Better HSCT practices and infectious disease prevention strategies have helped to reduce infectious complication rates at a major US transplant centre over the last decade. Data collected from over 2500 patients treated at the Fred Hutchinson Cancer Research Center, Seattle, showed a substantial reduction in infections for those treated from 2003-2007 compared with 1993-1997. Gram-negative bacteraemia fell from 15% to 8%, invasive mould infections from 9% to 7% and yeast infections from 9% to 1%. Dr Steven Pergam and co-

workers attributed the improvements to less use of bone marrow as the transplant source, more non-myeloablative transplants and better infection prophylaxis during the more recent time period.

Posaconazole prophylaxis in children

Promising results were reported for antifungal prophylaxis with posaconazole in 9 paediatric patients with acute leukaemia, aged 3-15 years, by Dr Helen Kennedy and colleagues at the Royal Hospital for Sick Children, Glasgow, UK. As the majority had previously experienced proven or suspected IFD, posaconazole was used as secondary prophylaxis to prevent recurrence following further courses of chemotherapy or HSCT. Treatment was well tolerated, and no recurrence occurred in 8 of the 9 patients. Twenty two posaconazole levels were measured, with a median level of 1.32 mg/l (range <0.125mg/l to 3.24mg/l). In four cases (18%) levels were below target, prompting a change from twice daily to four times daily dosing, with successful results.

Long term data support posaconazole prophylaxis

Standard long-term posaconazole prophylaxis can be safe and effective for prevention of IFD, and strategies to improve exposure to the drug, such as higher doses and administration with acidic drinks and nutritional supplements and reduction of proton pump inhibitor (PPI) usage, should be considered. These were the recommendations of Dr Drew Winston and colleagues from UCLA Medical Center, Los Angeles, USA, following an evaluation of oral posaconazole as standard antifungal prophylaxis in all adult allogeneic HSCT patients at the centre. Treatment was started on day 1 of HSCT and continued until day 100. Posaconazole was then continued in patients still requiring corticosteroids for prevention or treatment of graft versus host disease (GvHD). Breakthrough IFI occurred in 8/106 (7.5%) patients within six months of transplant, and three further patients developed infection 53-66 days after posaconazole prophylaxis was discontinued. IFI mortality was 3.7%. At 6 months after HSCT, overall survival was 65% and fungal free survival was 62%. The researchers concluded that development of an iv formulation could further enhance the efficacy of posaconazole.

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