

Highlights from the 5th Trends in Medical Mycology (TIMM) congress Valencia, Spain, 2-5 October 2011

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Invasive fungal disease: “know your enemy, know your goal!”

Rising numbers of immunosuppressed patients at risk of invasive fungal disease (IFD) and increasing yeast and mould resistance to anti-fungal agents are making it more important than ever to develop better ways to prevent and treat infections, based on local incidence and resistance rates.

At the 5th Trends in Medical Mycology (TIMM) congress in Valencia, Spain, over 1000 clinicians and research scientists joined forces to discuss how their growing understanding of the threat of IFD can help them refine their defense strategies.

High risk versus low risk

Identifying high risk patients who require anti-fungal prophylaxis is now a key priority for clinicians working in intensive care units (ICUs) as well as those treating patients more traditionally at risk for yeast and mould infections, such as leukaemia and bone marrow transplant patients.

Dr Luis Ostrosky-Zeichner (Memorial Hermann Texas Medical Centre, Houston, USA) reported latest progress in developing predictive risk scores for invasive candidiasis (IC) in ICU patients – now responsible for 5-10% of ICU-acquired infections, with mortality comparable to that of severe sepsis/septic shock¹. A risk score based on ICU stay for at least 3 days, mechanical ventilation, broad-spectrum antibiotics, and central venous catheter, together with at least one of: parenteral nutrition, dialysis, pancreatitis, systemic steroids, or other systemic immunosuppressive agents can identify patients at high risk (>10%) of IC, who benefit from caspofungin prophylaxis².

Although it is widely agreed that ICU, haemato-oncology and other patients with a 10% IFD risk require prophylaxis, many of those at intermediate risk (5-9%) probably need prophylaxis, pointed out Professor Catherine Cordonnier (Henri Mondor Hospital, Créteil, France), although she stressed that benefits are very dependent on local epidemiology. She drew attention to data from the SEIFEM Italian working group, presented at the congress, which demonstrated that local risk factors, such as the type of house in which patients lived,

home renovation or other nearby construction work, can influence risk of IFD – before hospital admission or treatment³. She also stressed the importance of deciding a “stopping time” for patients on prophylaxis – pointing out that, antifungal therapy should be seen as a bridge to immune recovery as patients do have to return and live in the “fungal world”. She advised delegates to “know your enemy, know your goal” in order to get the best from their management strategies.

New genetic insights

Growing understanding of genetic factors which predispose to IFD may also help determine which patients are most in need of prophylaxis and provide new targets for novel antifungal agents.

Dr Mihai Netea (Radboud University, Nijmegen, The Netherlands) presented data showing that patients with genetic variations in toll-like receptor 1 are nearly twice as likely to get candidaemia as those without the variation, and that this variation is associated with a reduction in pro-inflammatory cytokine production. Single nucleotide polymorphisms (SNPs) for interleukin (IL) 10 and 12 β have been associated with three and four fold increased risks of fungaemia and persistent reductions in interferon gamma, IL6 and IL8. Although much rarer, autosomal dominant chronic mucocutaneous candidiasis can have devastating consequences for families, so the recent discovery that mutations in the coiled coil (CC) domain of signal transducer and activator of transcription 1 (STAT1) lead to defective responses in type 1 and type 17 helper T cells (Th1 and Th17) may have important implications for future treatment⁴, suggested Dr Netea.

Combating fungal resistance

Clinicians need to be more vigilant in monitoring patients for drug-resistant strains of *Candida* and *Aspergillus* – in the light of increasing reports of clinically relevant azole and echinocandin resistance, warned Dr Susan Howard (University of Manchester, UK). She explained that the primary mechanism of azole resistance in *A. fumigatus* is amino acid substitutions in the protein, Cyp51A, which azoles target in order to block ergosterol formation for fungal cell walls. Three “hot spots” of mutations in the Cyp51A gene have been found at codons 54, 98 and 220, and patients can experience multiple, independent mutations resulting in recurrent bouts of resistant aspergillosis. Although most patients develop mutations within their lungs, evidence from some countries, notably The Netherlands, suggests that patients may acquire strains that are already resistant, possibly as a result of agricultural azole use.

Some mutations result in resistance to all azoles, while others only affect one or more drugs, so susceptibility testing is important as azole minimum inhibitory concentrations (MIC) predict outcome (though this is less clear with echinocandins).

However, as Professor David Denning (University of Manchester, UK) pointed out, susceptibility testing using culture methods can be slow and unreliable. He reported newly published data showing that an ultrasensitive form of real time polymerase chain reaction (PCR) assay for *Aspergillus* was able to detect azole-resistance mutations within Cyp51A in over half of bronchoalveolar lavage (BAL) samples which were culture negative⁵.

Paediatric considerations

Better survival rates for very premature babies and highly immunocompromised infants are resulting in growing IFD rates in the paediatric population, but diagnostic difficulties and a lack of paediatric indications for some key antifungal agents are significant challenges. Dr Emmanuel Roilides (Aristotle University, Thessaloniki, Greece) explained that *Candida* species are nearly always responsible for IFD in very premature babies, with two thirds of cases being *C. albicans* and around one in eight being *C. parapsilosis*, with *C. krusei* and *C. glabrata* found very rarely. *Candida* infection is also a significant problem in paediatric ICUs and in children undergoing gastrointestinal surgery, while *Aspergillus* species and other rarer filamentous fungi are more common in older children with immunodeficiencies or cystic fibrosis.

Professor Roilides pointed out that conventional culture and histological methods lack sensitivity and specificity in children. The latest recommendations from the European Conference on Infections in Leukaemia (ECIL) support serum galactomannan (GM) testing in BAL and cerebrospinal fluid with a cut-off value of 0.5, but evidence concerning use of β D glucan is very limited in children and mean levels are higher in immunocompromised children than adults. Pulmonary imaging can be useful, but halo signs seen in adults are rarely present in children and fluffy infiltrates are a more likely finding to support diagnosis.

Professor Roilides stressed that scaling adult drug doses to body weight and surface area is not appropriate as children are not “little adults”. Drugs are usually cleared more rapidly in children than adults; for example, larger doses of voriconazole are needed for children than adults. Professor Roilides recommended fluconazole prophylaxis for very low birth weight babies and in the neonatal ICU, and amphotericin B as first line treatment (or fluconazole if it has not been used in prophylaxis). Voriconazole is recommended as first line treatment for aspergillosis, except in under-2s.

Which antifungal drug levels predict efficacy?

Concerns that some patients do not achieve high enough plasma concentrations of antifungal drugs for effective prophylaxis and treatment are leading to increased use of therapeutic drug monitoring (TDM) so that doses can be tailored to individual needs. But, in an extensive review of data from posaconazole clinical trials, Professor Oliver Cornely (University Hospital of Cologne, Germany) questioned whether low blood levels always translate into increased risk of IFD, and suggested that intracellular concentrations rather than plasma levels may be more indicative of efficacy.

He explained that the results of a recent analysis of data from two pivotal trials of posaconazole prophylaxis which linked clinical failure to a plasma posaconazole level below 700 ng/ml were difficult to interpret⁶. He pointed out that, of the 15 cases of proven or probable IFD in the analysis, four patients were diagnosed days or weeks after the end of posaconazole prophylaxis, by which time their drug levels would have been very low or zero, and another patient had *Pneumocystis pneumonia* against which azoles have no activity. He also questioned the reliability of findings from a further three cases where pharmacokinetic samples used in the analysis were several weeks old.

Professor Cornely reported the results of a recent study which failed to show any significant effect of dose escalation above posaconazole 800mg per day on plasma levels in patients at risk of poor absorption due to diarrhoea or other factors. But he added that recent studies have shown high ratios of intracellular to extracellular posaconazole, both in blood cells⁷ and alveoli, suggesting that high intracellular concentrations may be more relevant to posaconazole efficacy and distribution than plasma levels.

Empirical versus pre-emptive treatment

The first patients will soon be randomised to a large EORTC phase III clinical trial to compare the effects of empirical vs. pre-emptive antifungal treatment in haematological malignancy and allogeneic HSCT patients. Dr Johan Maertens (University Hospital Gasthuisberg, Leuven, Belgium) told delegates that the study, which is expected to enroll over 500 patients from 10 countries, will address the continuing debate over whether clinical, radiological and/or biomarker-directed IFD diagnosis can reduce the burden of unnecessary treatment associated with empirical therapy.

In the study, patients will receive either empirical treatment with caspofungin if they have unexplained persistent fever unresponsive to, or recurring after antibiotics, or pre-emptive

treatment only when they have positive galactomannan, X ray or CT lesions, or positive culture of *Aspergillus sp.* The primary outcome is overall survival at 42 days.

Dr Maertens highlighted the significant gaps in evidence concerning empirical and pre-emptive (also called diagnosis-driven) treatment. He explained that previous clinical trials have shown that PCR-based pre-emptive treatment can result in greater use of antifungal agents than empirical treatment, with no impact on IFD⁸, while clinical criteria and risk factors can successfully predict need for antifungal therapy⁹, and treatment driven by positive high resolution CT (HRCT) findings¹⁰ or a combination of clinical, CT and galactomannan (GM) findings¹¹ can reduce antifungal usage without adversely affecting IFD mortality. However, “real world” observational data on infectious complications in patients with hematologic malignancies treated with chemotherapy and/or HSCT in Italy recently showed that IFD mortality was three times higher in patients treated pre-emptively (based on laboratory or radiographic signs) than those treated empirically on the basis of persistent fever without a known cause and unresponsive to antibiotics¹².

Dr Maertens concluded that “the jury is still out” over empirical versus diagnosis-driven treatment, and much continues to depend on local epidemiology, use of mould-active prophylaxis and availability of molecular, CT and other diagnostic tools.

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