Invasive Fungal Disease highlighted at the 22nd European Congress of Clinical Microbiology and Infectious Diseases, London, UK, 31 March – 3 April 2012

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Antimicrobial stewardship is key in fight against fungal resistance

Antimicrobial stewardship initiatives aligned to the World Health Organisation's global campaign to safeguard antimicrobial medicines for future generations provided a major focus for the 22nd European Congress of Clinical Microbiology and Infectious Diseases, held in London, UK.

In an era of finite resources and limited antimicrobial development, speakers at the conference consistently highlighted the importance of preserving the effectiveness of current treatments.

Dr Klaassen reported results of a recent study in which a novel mixed-format real-time polymerase chain reaction (PCR) assay was used to identify wild type cyp51A and point mutations conferring azole resistance in *A. fumigatus* isolates[2]. Hybridisation of a single strand DNA detection probe with single strand target gene DNA enabled the researchers to differentiate between susceptible and resistant strains, using fluorescent dyes. Four triazole-resistant isolates were identified, all of which contained an identical combination of mutations leading to multi-triazole resistance, and molecular testing results were totally concordant with phenotypic susceptibility testing.

However, as Dr Klaassen pointed out, for each AF group of drugs there are multiple potential resistance mechanisms including large numbers of point mutations, not all of which confer resistance, and this makes real-time direct detection very difficult. He suggested focusing on species, such as *A. fumigatus* and *Candida*, which are well studied, and using blood rather than other fluid samples, on the basis that if an organism is detectable in serum it is the most likely source of relevant infection.

Concerns over AF resistance

Growing prevalence of harder-to-treat, non-albicans strains of *Candida,* and the potential for spread of azole resistance outside current northern European hotspots headed the list of epidemiological concerns about IFD discussed at ECCMID.

Dr Jesús Guinea Ortega, from the Hospital General Universitario Gregorio Marañón, Madrid, Spain, explained that, while *Candida glabrata* is a problem in many countries, *C. parapsilosis* is a growing challenge for clinicians in Spain. In the multicentre CANDIPOP surveillance study in Spain, reported at the conference, *C. albicans* was present in 46% of isolates from 729 candidaemia patients, followed by *C. parapsilosis* in 25% and *C. glabrata* in 14%. Antifungal susceptibility was tested in 650 isolates and the overall rate of fluconazole resistance (MIC>4mcg/ml) was 14.6%. Overall mortality was 38%, with the highest rate in the 2% of patients with *C. krusei.* Removal of central venous catheter (CVC) within the first 48 hours of infection was critical for preventing early mortality.

Turning to azole resistance in aspergillosis patients, Dr Guinea Ortega highlighted the widespread azole resistance reported recently in The Netherlands, and linked to agricultural use of azole fungicides[1]. Amongst over 2000 isolates tested in 1,385 patients, the prevalence of itraconazole resistance in *Aspergillus fumigatus* was 5.3%, with levels ranging from 0.8%–9.5% across the country. Patients with a haematologic or oncologic disease were at greatest risk of itraconazole-resistant infection, and 64% of patients with resistant isolates were azole naïve. Mortality in patients with resistant isolates was 88%.

Dr Guinea Ortega concluded that environmental factors are important for AF resistance and recommended that resistance rates in candidaemia and aspergillosis patients should be carefully monitored.

Is direct detection of antifungal resistance possible?

Real-time, direct detection of AF resistance in clinical specimens is challenging but not impossible, though a clear strategy is needed for target selection, concluded Dr Corne Klaasen, from Canisius Wilhelmina Hospital, Nijmegen, The Netherlands. He explained that development of rapid, molecular-based detection methods need to take account of the resistance mechanisms of different AF groups of agents. For example, with azoles, there are four main resistance mechanisms – point mutations in or increased expression of target genes (cyp51A in *Aspergillus* and erg 11 in *Candida*), increased expression of efflux pumps, and species specific intrinsic resistance.

Which drug for antifungal prophylaxis and treatment?

A systematic review of clinical trials of primary AF prophylaxis for patients undergoing allogeneic haematopoietic cell transplantation (alloHCT) has concluded that voriconazole and posaconazole are better choices than itraconazole. The review, presented jointly by leading investigators involved in the key trials on which the analysis was based, compared proven/probable IA at day 180 from five AF prophylaxis studies[3-7]. This showed that voriconazole prophylaxis had an 85% probability of a favourable outcome relative to fluconazole, compared to 80% for posaconazole and 69% for itraconazole. Posaconazole had a 45% probability of achieving the lowest IA rate of the four agents, compared to 42% for voriconazole and 10% for itraconazole. The group concluded that, in the absence of data on the comparative efficacy of voriconazole and posaconazole, ease of use, fungal species susceptibility and cost are likely to determine the final decision.

Evidence of the cost effectiveness of posaconazole was provided by a study carried out at the University of Cologne, Germany, which compared the costs of posaconazole prophylaxis and topical polyene prophylaxis in "real world" patients with acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS). Average costs were € 21,040 and €23,169, respectively. While AF costs were slightly higher in the posaconazole group, the costs of concomitant antibacterials and antivirals were lower with posaconazole, and patients taking posaconazole required shorter intensive care unit (ICU) stays (1.79 vs 3.83 days).

In a further analysis, the same researchers compared the costs of treating candidemia in ICU patients, using newer agents (echinocandins, liposomal amphotericin B, or voriconazole) or conventional AFs (amphotericin B deoxycholate or fluconazole). Patients treated with the newer agents tended to be sicker and more likely to have non-albicans *Candida* infection. Total direct costs of treatment were €41,060 and €28,885 respectively, while indirect costs per patient due to illness-related lost productivity were similar (€1,202 vs €1,087). Similar numbers of patients in the two groups survived hospitalisation (56% and 50% respectively) and one year after diagnosis (44% and 33%), and the researchers concluded that outcomes for sicker patients treated with newer AFs were similar to those achieved with less sick patients treated with conventional drugs.

Latest insights into azole dose adjustment

A decision-support software controller to improve therapeutic drug monitoring (TDM) for voriconazole has shown promise for optimising dosage adjustment to achieve predefined serum concentration targets. Professor William Hope, from the University of Manchester, UK, presented data showing that the RightDose programme accurately predicted

voriconazole dosages required to achieve a predefined serum trough concentration of 1mg/l for individual patients. Recently published pharmacokinetic data from 64 healthy volunteers and patients with proven/probable IA treated with voriconazole[8] were used to develop the programme which was then used to predict the concentration-time profile of each of 10 HSCT patients who had received a standard voriconazole regimen during a safety and pharmacokinetics study[9]. A good match was achieved between the doses predicted by the programme to achieve a predefined trough concentration of 1mg/l, and those actually recorded in the HSCT study. Professor Hope explained that the process of dosage optimization could begin with the first dosing interval, meaning that therapeutic and nontoxic serum concentrations can potentially be achieved in the first 48-71 hours of dosing.

Recent research suggests that intracellular levels of posaconazole may be more relevant to therapeutic efficacy than serum levels. A Canadian/US research group – which had previously demonstrated that the drug was found mainly within host cell membranes in concentrations sufficient to inhibit growth and prevent fungal damage[10] – presented new research at ECCMID, showing that posaconazole concentrates specifically to the endoplasmic reticulum (ER) within host and fungal cells, a structure where the cyp51A target for posaconazole is also known to be located.

Update on newer antifungals

Limited progress was reported in the development of new AFs at this year's ECCMID, but Professor Dimitrios Kontoyiannis, from the MD Anderson Cancer Centre, Houston, Texas, highlighted the novel oral glucan synthase inhibitor, MK3118, as one of the most promising agents in development. He explained that MK3118 is active against both *Candida* and *Aspergillus*, and has demonstrated *in vitro* inhibition of glucan synthesis comparable to that of caspofungin. In a Phase 1 multi-dosing study, MK3118 was found to be well tolerated in doses up to 800mg for up to 28 days, with a favourable pharmacokinetic profile.

Professor Kontoyiannis reported that phase 2/3 studies are underway comparing a novel oral formulation of posaconazole with intravenous treatment in patients at high risk of IFD. This follows healthy volunteer studies showing good systemic exposure with oral posaconazole, with or without food, and dose-finding studies favouring a 300mg daily dose. Professor Kontoyiannis also reviewed studies of the new azole, isavuconazole, showing high bioavailability for the oral capsule, with no effect of food or acid suppression, and once daily dosing. He added that that isavuconazole is active against *Candida* and *Aspergillus* infection, with modest activity against *Rhizopus* and *Scedosporium*.

Professor Kontoyiannis concluded that an orchestrated strategy is needed to develop good biomarkers for measuring the efficacy of novel AF approaches, such as vaccines and antibody treatment, if more rapid progress is to be achieved.

Dr Francesco Menichetti, head of the Infectious Diseases Unit, Nuovo Santa Chiara Hospital, Pisa, Italy, proposed that key goals of antifungal (AF) stewardship programmes should include improved clinical outcomes, avoidance of adverse drug-related events, reduced emergence of resistance and control of costs. He stressed the need for prompt treatment for invasive fungal disease (IFD) but urged a move towards more targeted empirical therapy, based on greater diagnostic accuracy, with better serology, and treatment recommendations tailored to individual patients.

Data from an AF stewardship programme at the University of Nice, Sophia Antipolis, France, presented at the congress, showed the impact of a multidisciplinary AF management team on clinical outcomes and AF use. Between 2005 and 2010, 636 AF prescriptions were discussed by the AF team and advice was fed back to physicians in over half of the cases. During that time, there was a gradual improvement in compliance with IFD management recommendations, such as use of diagnosis tools, choice of first line AF agent, and IFD follow up, with an accompanying increase in favourable outcomes from 60% to 87% for aspergillosis and from 78% to 95% for candidaemia. Total AF use and costs were stabilised, and the researchers proposed that routine defined daily dose (DDD) monitoring should be carried out for AF agents, and not just limited to antibiotics, in order to aid benchmarking.

Additional support for AF stewardship initiatives came from Professor Oliver Cornely who reported a rapid increase in electronic requests for advice after an infectious disease consulting service (IDCS) was made available to all specialties within the University Hospital of Cologne, Germany. At 1400 per year, the annual number of requests is equivalent to one for each of the hospital's beds, and additional staff members are now needed to meet demand for the service. Dr Cornely explained that about half of requests are made by surgical disciplines, and the most typical advice given by the IDCS to clinicians is to stop anti-infectives, adjust dose, focus treatment or make a proper diagnosis for the infection being treated. He added that an unexpected spin-off from the service has been identification of unmet medical needs requiring further clinical trials.

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