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Meeting report

Current challenges in the diagnosis and management of invasive fungal infections: report from the 15th International Symposium on Infections in the Immunocompromised Host: Thessaloniki, Greece, 22–25 June 2008

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ABSTRACT

New, aggressive forms of immunosuppression and an increasing population of patients at risk provide fertile ground for opportunistic invasive fungal infections (IFIs). Particularly challenging is the changing epidemiology of IFIs: rare pathogens are now more common and resistant strains are emerging among species that are generally considered to be sensitive. Staying one step ahead of this evolving epidemiology is a major task and some 400 delegates, from 44 countries, learned that although there has been considerable progress, more is needed.

1. Epidemiological trends

The incidence of invasive fungal infection (IFI) has increased over the last 10 years, with more unusual fungal pathogens gaining prominence. Prof. George Petrikkos, from the University of Athens, Greece, told the meeting that without effective prophylaxis, invasive aspergillosis (IA) occurs in ca. 10–15% of allogeneic haematopoietic stem cell transplantation (HSCT) recipients, in 10% of patients with acute myeloid leukaemia (AML), in 5% with acute lymphoblastic leukaemia and in 2% receiving autologous HSCT. He presented data from the US Transplant-Associated Infection Surveillance Network (TRANSNET) for 2001–2006, indicating that *Aspergillus fumigatus* accounts for approximately one-half of all isolates and *Aspergillus flavus*, *Aspergillus niger* and *Aspergillus terreus* for 9%, 7% and 5%, respectively [1].

Patterns of candidiasis have also changed, Prof. Petrikkos explained, with significant decreases and increases, respectively, in bloodstream infections due to *Candida albicans* and *Candida glabrata* over time [2]. He reported that *C. glabrata* accounted for 32% and *C. albicans* for only 22% of all IFIs. Other data indicate an increasing contribution from *Candida parapsilosis*, from 0–5% in 1998–2001 to ca. 15% in 2003 [3]. Increases in azole prophylaxis and the widespread use of antifungal agents to treat febrile neutropenia may all be responsible for the observed shifts in *Candida* spp., according to Prof. Petrikkos.

The emergence of previously rare fungal species is a particular cause for concern, with that of zygomycetes linked to prolonged voriconazole (VCZ) use [4]. Prof. Petrikkos noted that zycomycetes accounted for ca. 24% of all invasive mould infections in transplant recipients by early 2006 and that infections caused by *Fusarium* and *Scedosporum* spp. are also increasing in incidence [5]. Ongoing projects to elucidate further the emerging epidemiology of previously uncommon fungal infections include a European registry of the European Confederation of Medical Mycology Working Party on Zygomycosis (http://www.ecmm.org) and a global internet registry based at the University of Cologne, Germany (Fungiscope; http://www.fungiscope.net) that is collecting data on infections due to emerging fungal pathogens.

Whereas mortality of IFIs due to candidosis is falling, that due to aspergillosis and other mycoses is increasing, Prof. Petrikkos said. He pointed out that a 2006 survey of nearly 12 000 patients from 18 centres showed an overall mortality of 42% for *Aspergillus* spp., 64% for zygomycetes and 52% for *Fusarium* spp. [6].

2. At-risk groups

Aggressive immunosuppressive therapy is now used in a wide variety of patients, including those with transplant rejection or severe graft-versus-host disease (GvHD), haematological or other cancers, and autoimmune disorders (e.g. rheumatoid arthritis, ulcerative colitis, Crohn's disease, multiple sclerosis). Several speakers highlighted increases in IFI in patients receiving antithymocyte globulin, monoclonal anti-lymphocyte antibodies such as alemtuzumab and natalizumab, or tumour necrosis factor-alpha blockade with infliximab, etanercept or adalimumab. These observations point to the importance of T-cell function and innate effector molecules for adequate host defence against opportunistic fungal pathogens. The probability of an IFI in an individual patient thereby increases with the number of risk factors, the most important being the net state of phagocyte impairment and the disruption of skin or mucosal barriers. The most vulnerable patient groups are therefore those with hereditary defects of phagocytosis such as chronic granulomatous disease (CGD) or those receiving treatment for severe GvHD following allogeneic HSCT: without prophylaxis, >50% of patients with CGD and >60% of those with grade III/IV GvHD will develop an IFI, reported Prof. Georg Maschmeyer (Klinikum Ernst von Bergmann, Potsdam, Germany).

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2.1. The paediatric population

Prof. Andreas Groll (University Children's Hospital, Münster, Germany) discussed the epidemiology and risk factors in children. Data from single-centre series indicate a frequency of IA in paediatric patients at risk of 4.5–10%, with associated crude mortality rates of 40–94% [7]. Based on discharge data in 2000, the annual incidence of aspergillosis was 0.4% among hospitalised immunocompromised children in the USA, with an overall in-hospital annual mortality of 18% [8]. Most cases of paediatric IA present as invasive pulmonary infections, which carry an approximate 30% risk of dissemination to the central nervous system. *Aspergillus fumigatus* is the most common cause of disease worldwide, followed by *A. flavus*, *A. niger* and lastly *A. terreus*, which is less susceptible than the others to amphotericin B (AmB).

The incidence of invasive candidiasis (IC), as revealed in discharge data from US hospitals in 2000, is even higher in children than in adults (47 vs. 30 per 100 000). It is especially high in neonates (150 per 100 000) and is much more common indeed than meningococcal infections (0.5–5.0/100 000) [9,10]. *Candida* spp. now account for 9–13% of all bloodstream isolates in neonatal Intensive Care Units (ICUs); the associated crude mortality is 15–30% and the attributable mortality is 6–22%, despite appropriate therapy. The overall frequency of IC in children with high-risk leukaemias and/or undergoing HSCT is 8–10%, with a crude mortality of at least 20%, approaching 100% in patients with persistent neutropenia [7].

Zygomycoses are characterised by highly aggressive tissue growth, leading to a fulminant presentation and high mortality rates (61% overall and 79% in neonates in a recent study [11]). The incidence of disseminated disease and the mortality rate both appear to be higher in paediatric than adult patients.

Candida and *Aspergillus* spp. as well as other opportunistic yeasts and moulds are most frequent in children with phagocytosis defects or mucosal or skin barrier breakdown; *Cryptococcus neoformans* and dimorphic fungi are more common in those with deficiencies of acquired immunity. High-risk patient groups for opportunist fungal infections include: premature neonates; critically ill surgical patients (especially those undergoing abdominal surgery); patients in ICUs and/or with implants or burns; children who have congenital immunodeficiency or human immunodeficiency virus (HIV) infection; those with malignancy-associated neutropenia or undergoing HSCT or solid organ transplantation; and patients receiving corticosteroids or some of the newer immunosuppressants. Among neonates, prematurity, prolonged rupture of membranes, intubation, use of H2 blockers and third-generation cephalosporins all increase the risk of IC [7].

3. Diagnostic methods

The difficulties of diagnosing IFI against a shifting epidemiological background were outlined by Prof. Per Ljungman (Karolinska University Hospital, Stockholm, Sweden), who emphasised that prompt targeted therapy could cut mortality. However, all current methods have important limitations, he said. Computed tomography (CT) scanning in patients with suspected aspergillosis has made diagnosis quicker and has reduced mortality. In one report, patients with the pathognomonic radiographic 'halo' sign had a better prognosis than those without it [12]. However, this sign is unspecific, absent in more than one-third of those with proven or probable pulmonary aspergillosis, and of a temporary nature. Detection of *Aspergillus* spp. in bronchoalveolar lavage fluid by culture or galactomannan assay has a high predictive diagnostic value. Histopathology can eliminate a non-infectious aetiology and may be positive even when cultures are negative; it may be complemented by polymerase chain reaction (PCR)-based molecular diagnostic methods [13]. Prof. Ljungman explained that the enzyme-linked immunosorbent assay (ELISA) for galactomannan in blood, used to help identify *Aspergillus* infections, is limited by variable sensitivity, false-negative results in patients receiving agents with anti-mould activity [14], and false-positive results in those on piperacillin/tazobactam, an agent commonly used in febrile neutropenic patients [15]. Cryptococcal infections and zygomycoses evade detection by the (1,3)-β-D-glucan ELISA, a blood-based assay that does not allow for differentiation of fungal pathogens and is not well validated but may be useful for pre-emptive strategies [16]. Finally, he noted, DNA assays in blood using PCR still lack clinical validation and standardisation.

In children, diagnosis can be even more difficult. In a recent multicentre survey [17], only 8% of paediatric patients with aspergillosis exhibited the halo or air-crescent signs, said Prof. Groll. Galactomannan ELISA data are scarce in children, but the assay appears to be less sensitive than in adults, with higher false-positive rates (10.1–44% vs. 0.9–2.5%) and high false-negative rates in some subgroups, as reported by Prof. Emmanuel Roilides (Aristotle University, Thessaloniki, Greece). He added that PCR data are also limited in the paediatric patient population [18].

Combining the different methods may assist accurate diagnosis. This strategy reduced the need for empirical antifungal therapy in one institution from 35% to 7.7% and detected all cases of IA and other IFIs, apart from one case of zygomycosis. Survival at 12 weeks for patients with aspergillosis was 63.6% [19]. However, not all centres have the appropriate resources to emulate this approach, Prof. Ljungman conceded. This provides the rationale for antifungal prophylaxis, as discussed below.

4. Treatment challenges

Established antifungal agents are proving less than effective against some of the emerging species. Of all the available agents, only AmB and posaconazole (PCZ) cover virtually all the important fungi. However, AmB minimum inhibitory concentrations for *C. glabrata* and *C. albicans* are higher than previously, reported Prof. Petrikkos. Fluconazole (FLZ) and itraconazole (ITC) resistance has reached 10–15% among *C. glabrata*, with one-half of all strains showing dose-dependent susceptibility. Thus, whilst current guidelines list FLZ, AmB, echinocandins and VCZ as the preferred treatments for IC before species identification [20,21], the choice depends on the patient and the local epidemiology. Similar considerations are important in the treatment of IA, for which both European and American guidelines recommend VCZ as a first-line therapy, with lipid formulations of AmB as an alternative [20,22]. However, prolonged VCZ use may be responsible for the emergence of zygomycetes as important pathogens, as Prof. Petrikkos pointed out. A much discussed approach to improve the still poor outcome, particularly of IA, is to use two agents in combination. Although some combinations showed synergistic or additive effects in preclinical studies, others are antagonistic and there are no clinical data as yet to support the general use of combination therapy, he said. Lipid formulations of AmB are the preferred treatment for zygomycoses, with evidence to support PCZ as salvage treatment [20], he noted.

4.1. Treatment in children

The evidence base for IFI treatment in children is less robust than in adults, although experience is growing. Dr Theoklis Zaoutis (The Children's Hospital of Philadelphia, Philadelphia, PA) explained that