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Review

The PATH (Prospective Antifungal Therapy) Alliance® registry and invasive fungal infections: update 2012☆

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ABSTRACT

The Prospective Antifungal Therapy Alliance (PATH Alliance®) performed prospective surveillance of invasive fungal infections (IFIs) among patients hospitalized at 25 medical centers in North America between 2004 and 2008, collecting information on the epidemiology, diagnosis, treatment, and mortality rates of IFIs. In total, 7526 IFIs were identified in 6845 patients. *Candida* spp. (73.4%) were the most common pathogens, followed by *Aspergillus* spp. (13.3%), and other yeasts (6.2%). Culture was the most frequently used diagnostic test in the majority of IFI categories. Most patients with invasive candidiasis were treated with fluconazole (48.3%) and the echinocandins (34.0%), while voriconazole (45.5%) was the main antifungal agent for invasive aspergillosis. The 12-week survival rate ranged from 37.5% for hematopoietic stem cell transplant recipients to ~75.0% for those with HIV/AIDS. In summary, the findings of the PATH Alliance® registry provide a better understanding of the epidemiology of a vast variety and large numbers of IFIs.

1. Introduction

Invasive fungal infections (IFIs) have emerged as major causes of morbidity and mortality, in particular among patients who are immunocompromised or hospitalized with serious underlying diseases (Horn et al., 2009b; Kollef et al., 2008; Kontoyiannis et al., 2010; Lockhart et al., 2009; Neofytos et al., 2009; Pappas et al., 2010; Perlroth et al., 2007; Pfaller and Diekema, 2010; Richardson and Lass-Flörl, 2008). High-risk groups include individuals undergoing hematopoietic stem cell transplantation (HSCT), solid organ transplantation (SOT), or major surgery (especially gastrointestinal surgery); those with AIDS, neoplastic disease, immunosuppressive therapy, or advanced age; and premature babies (Arendrup et al., 2011; Fishman, 2007; Fridkin et al., 2006; Kontoyiannis et al., 2010; Méan et al., 2008; Morris et al., 2008; Neofytos et al., 2009; Neofytos et al., 2010; Pappas et al., 2010; Perlroth et al., 2007; Pfaller and Diekema, 2010; Procop and Roberts, 2004; Singh, 2003; Singh et al., 2008; Zaoutis et al., 2005; Zaoutis et al., 2007).

Despite the significant progress attained in the field, the prevention, diagnosis, and therapy of IFIs remain extremely difficult. Effective management of IFIs requires reliable information on their epidemiology and associated risk factors, early diagnosis, susceptibility to antifungal agents, and timely initiation of appropriate treatment. Randomized clinical trials (RCTs) remain the gold standard for the establishment of optimal treatment of IFIs. Unfortunately, RCTs are often limited in the information they can provide due to an inability to enroll sufficient numbers of patients, particularly for the rarer IFIs, and due to heterogeneity of the underlying diseases (Anaissie, 2007). Furthermore, most RCTs do not provide sufficient data on the most severely ill and immunocompromised patients and, thus, may not always represent the "real-world" experience of physicians who manage such patients (Anaissie, 2007). To fill this void, one approach has been to turn to analysis of large databases or fungal registries to provide relevant medical information (Baddley et al., 2011; Horn et al., 2009b; Kontoyiannis et al., 2010; Neofytos et al., 2009; Pappas et al., 2010; Park et al., 2011; Zaoutis et al., 2005).

The Prospective Antifungal Therapy Alliance (PATH Alliance®) was established in 2004 in order to perform prospective surveillance of all IFIs among patients hospitalized at selected tertiary care medical centers in North America. Its aim was to improve the understanding of the burden of IFIs in different patient groups, better define patients at risk, and understand current approaches to the diagnosis and treatment of IFIs (Horn et al., 2007c). The PATH Alliance® consists

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of 25 tertiary-care medical centers in the USA (23 centers) and Canada (2 centers; Fig. 1).

Since its launch in July 2004, 6918 (6845 eligible for evaluation) patients have been enrolled in the registry, and multiple articles, abstracts, and presentations have been published giving valuable insights into the epidemiology, diagnosis, underlying conditions, fungal species, outcomes, and therapy of IFIs (Davis et al., 2009; Fishman et al., 2005a, 2005b; Horn et al., 2006a, 2006b, 2007a, 2007b, 2007c, 2007d, 2008a, 2008b, 2008c, 2009a, 2009b, 2009c; Klevay et al., 2008, 2009; Neofytos et al., 2007a, 2007b, 2009, 2010; Olyaei et al., 2008). The last patient data were entered into the registry on September 30, 2008, and the database was sealed on December 31, 2008. In this review, an overview of the results from the entire 5-year prospective PATH Alliance® survey is reported, summarizing the additional knowledge that has been gained concerning the epidemiology, species distribution, underlying conditions, treatments, and outcomes of IFIs from the 25 study sites.

2. Methods

Full details of the development of the program and its data collection methods have been published previously in the literature (Horn et al., 2007c). Briefly, patients with a diagnosis of proven or probable IFI were enrolled and followed prospectively for 12 weeks. Data on IFIs were collected using a real-time web-based electronic case report form. Data were recorded to gain information on 4 research themes, namely, epidemiology, diagnosis, treatment, and outcome of IFIs. In order to address these topics, patient characteristics such as demographics, comorbidities, and administration of antifungal therapy before the diagnosis of IFI were recorded together with assessment of organ function, immunologic risks, and information on recent viral and bacterial infections. Detailed information on the IFI was collected, including the organism and species, diagnostic tests, antifungal therapy history, and other therapeutic procedures. Collection of patient data was via observational means and did not involve clinical interventions. The data entry procedure was designed to be efficient and intuitive, while various software features checked data quality at the point of entry; an audit trail was maintained in order to track all data entries and subsequent edits.

Medical centers were chosen for participation based on the number of patients treated for IFIs per year, and on the geographical and host diversity. Participating centers included those providing specialty care, such as SOT, HSCT, general oncology, and those caring for adult and pediatric patients. In total, there were over 39 lead investigators involved in collecting data for the PATH Alliance® registry, based at various centers in the USA and Canada.

All patients with a diagnosis of proven or probable IFI were eligible for enrollment. The classification of patient diagnoses into proven or probable IFI categories was based upon published consensus definitions (Ascioglu et al., 2002). Although these definitions were revised in 2008 (De Pauw et al., 2008), the registry was created and the database was sealed prior to the publication of the new criteria. All study sites identified patients in a number of ways, including review of reports from hospital departments such as microbiology, pathology, or pharmacy; the investigators' own patient base; and referrals from other physicians or departments. Patients were followed prospectively for 12 weeks following diagnosis, but participating sites also had the option to enter follow-up data at 6 months where patient records were complete.

Descriptive analyses were used for epidemiology, diagnostic measures, and antifungal therapy. Descriptive survival analysis was performed based on the whole patient group and for subpopulations. Survival distribution was estimated using the Kaplan–Meier method; patients who were lost to follow-up before the Week 12 assessment were censored on the day of their last activity documented in the database. Statistical analyses were performed using SAS version 9.2/ Enterprise Guide 4.2 (SAS Institute, Carey, NC, USA).

3. Results

3.1. Epidemiology

Upon completion of the survey in December 2008, 6918 patients had been prospectively enrolled by 25 centers into the registry. A total of 6845 patients with 7526 IFIs (proven: $n = 6647$, 88.3%; probable:

Fig. 1. Geographic location of participating sites.