Continuous Surveillance of Invasive Fungal Infection: A Realistic Goal for the Near Future

To the Editor—Using the Prospective Antifungal Therapy (PATH) Alliance registry, Neofytos et al. [1] investigated the epidemiology and outcome of invasive fungal infections (IFIs) in hematopoietic stem cell transplant (HSCT) recipients. Because use of Web-based registries is pivotal for progress in understanding IFIs, the Italian Hema e-Chart Group is also engaged in a prospective, multicenter, observational study designed to analyze all febrile events in patients with hematological malignancies (L.P., M.C., and A.N., unpublished data). Hema e-chart prospectively collects high-quality data derived from clinical experience and provides information on epidemiology and prophylactic and/or therapeutic drug use for IFIs. Distribution of investigating centers across Italy and a potentially large patient cohort facilitate the study of IFIs and the identification of appropriate subgroups for diverse research interests.

Starting in March 2007, each patient who has a newly diagnosed malignancy and all those who undergo HSCT are censored to assess IFI epidemiology. In December 2008, 25 centers were active, 4403 patients were enrolled (3243 patients who received new diagnoses and 1160 HSCT recipients), and 1173 febrile events had been registered. Interim analysis of HSCT recipients shows a 43% incidence of febrile events per population (34% and 65% in autologous and allogeneic HSCT recipients, respectively), a 5% incidence of fungal infection per population, and a 13% incidence of fungal infection per event (5% and 23% in autologous and allogeneic HSCT recipients, respectively). Our current fungal mortality rate is 35%.

These findings are different from those of the PATH Alliance, but because that study lacked a denominator, such as Hema e-chart’s pool of censored patients, the authors only counted the number of infectious episodes. They admitted that the incidence of IFI could not be calculated because the total number of transplants performed at each center was not recorded, but they concluded that invasive aspergillosis was stable, a downward trend emerged in invasive candidiasis, and Zygomycoses infections were increasing. Because no details were given on antifungal prophylaxis and treatments, it is hard to concur with the authors that the good response rate to antifungal therapy was a result of voriconazole use, because other antifungal drugs and combinations thereof were also administered.

The PATH Alliance investigation had the merit of trying to monitor IFIs prospectively but reported only outcomes of invasive aspergillosis after bone marrow or peripheral blood transplantation. Cord blood transplantation and IFIs due to other fungi were excluded. Although the study was defined as being multicenter, 147 of the 234 patients were enrolled by 2 centers, and almost 50% of allogeneic HSCTs and 68.5% of autologous HSCTs were performed by single centers, which the authors stated “may have skewed the presented outcomes and created further biases” [1, p. 271].

Unlike other epidemiological analyses, no difference emerged at 6 weeks after transplantation in IFI incidence or outcomes, regardless of whether the stem cell source was allogeneic or autologous [2, 3]. Intervals from HSCT to IFI were similar, but some IFIs were reported as late as 6 years after autologous transplantation. We do not know whether CD34+ cells were selected for autologous grafts, implying extensive T cell depletion, or why 75.3% of autologous HSCT recipients received steroids. Only neutrophil counts were monitored, and no information was given on lymphocyte reconstitution. Whether changes in physicians’ attitudes or changes in IFI epidemiology are responsible for these unexpected results is unclear.

Acknowledgments

Potential conflicts of interest. All authors no conflicts.

References


Reply to Pagano et al.

To the Editor—It was with great interest that we read the thoughtful comments by Pagano et al. [1] on our recent publication entitled “Epidemiology and Outcome of Invasive Fungal Infections in Adult Hematopoietic Stem Cell Transplant Recipients: Analysis of Multicenter Prospective Antifungal Therapy (PATH) Alliance Registry” [2]. The PATH Alliance is a prospective, multicenter, observational registry that collected data on the epidemiology, diagnosis, treatment, and outcomes of invasive fungal infections (IFIs) in the United States and Canada [3]. The PATH Alliance recorded information for all hospitalized patients with IFI from 23 major academic institutions from 2003 through 2008 [3]. As was noted, the study design prevented accumulation of detailed clinical data on all inpatients from each of the 23 tertiary care centers. The absence of a
denominator is a significant limitation of this registry, and as a result, it is not feasible to calculate the incidence of IFI among different transplant categories and overall.

Pagano et al. [1] report a “fungal mortality rate” of 35% for hematopoietic stem cell transplant (HSCT) recipients with IFI; it is not clear whether this is crude or attributable mortality. We reported an overall, crude mortality of 46.7% among HSCT recipients with IFI, which was estimated after exclusion of 35 patients who were lost to follow-up at 12 weeks. If these patients were not excluded, the estimated overall mortality would be lower (39.7%; 99 of 234 patients died). In fact, the 12-week mortality among HSCT recipients with invasive aspergillosis was as low as 35.5%. As discussed in our study, the improved rate of survival observed among patients with invasive aspergillosis is most likely the result of a combination of variables, rather than the effect of antifungal therapy alone [2]. We reported similar survival between allogeneic and autologous HSCT recipients with IFI. The majority (68.5%) of autologous HSCT recipients included in our study were reported by a single center and appeared to be high-risk patients (percentage with multiple myeloma, 68.5%; relapse of underlying disease, 60.3%; history of prior HSCT, 56.2%; and receipt of corticosteroids, 75.3%). A small number of autologous HSCT recipients received T cell–depleted or CD34+–selected grafts, as detailed in table 1 of our study [2]. These variables might have had an impact on our results. As was noted, this observation raises possible concerns about biases introduced by the enrollment of a substantial number of patients by a limited number of centers. This potential limitation of many multicenter studies [4] is offset to a degree by secondary survival analyses performed after exclusion of patients whose data were contributed by the highest-enrolling center.

We observed stable numbers of cases of invasive aspergillosis, with an increasing frequency of IFI due to Zygomycetes species and other molds, during the study period (figure 1). This observation is consistent with other single-center reports [5, 6]. The results for all HSCT recipients with IFI were presented in this study; however, univariate and multivariate analyses were performed only for allogeneic HSCT recipients with invasive aspergillosis—note that cord blood as a stem cell source was captured but was excluded from analyses because of the small number of patients.

Acknowledgments
We acknowledge Astellas Pharma US (APUS), for their generous support; Axiom Real-Time Metrics, for their expertise in registry management; and the many dedicated coordinators at each site. Financial support. As the financial sponsor of the PATH Alliance, APUS observed but did not influence the design of the PATH Alliance registry by the independent scientific advisory board. APUS contracts Axiom Real-Time Metrics to provide overall management services for the PATH Alliance registry, comprising data management, site support, application and database hosting, administrative management, and data extraction and analysis. APUS also sponsored Axiom Real-Time Metrics’s services for this individual research project; these services consisted of data extraction, facilitation of statistical analyses, preparation of figures, and manuscript review.

Potential conflicts of interest. D.N. has received grant support (for educational research) from Astellas. D.H. has received recent research funding from Astellas and past funding from Pfizer; has served as a consultant or advisor for Astellas and Pfizer; has been on the speaker’s bureau for Pfizer and Astellas; and has received speaking honoraria from Roche. E.A. has been a consultant and on the speaker’s bureau for Astellas, Pfizer, Gilead, Merck, and Schering-Plough. W.S. has served as consultant for Pfizer, Astellas, and Schering-Plough and has served on the speakers’ bureau for Astellas, Merck, and Pfizer. A.O. has been on the speakers’ bureau and has served as consultant for Pfizer and Astellas. J.F. has been a consultant for Merck, Hoffman LaRoche, Astellas, and Primerica; has received grant support (for educational research) from Astellas; and has been on the speakers’ bureau for Astellas and Roche. M.P. has been a consultant and on the speakers’ bureau for Pfizer, Astellas, Merck, and Schering-Plough. C.C. has served as a statistical consultant for Pharmacia, Pfizer, and Eli Lilly; as marketing analytics consultant for Roche; and as statistical consultant via third parties for Astellas, Topigen, and AstraZeneca. K.W. has had contract work with Astellas. K.M. has been a consultant and/or part of advisory boards for Astellas, Enzon, Merck, Pfizer, and Schering-Plough and has received grant support from Astellas, Enzon, Merck, and Pfizer.

D. Neofytos,1,2 D. Horn,3 E. Anaissie,3 W. Steinbach,4 A. Olyaei,3 J. Fishman,4 M. Pfaller,5 C. Chang,4 K. Webster,6,7,8 and K. Marr1,9
1The Johns Hopkins University, School of Medicine, Baltimore, Maryland; 2Thomas Jefferson University Hospital, Philadelphia, Pennsylvania; 3University of Arkansas for Medical Sciences, Little Rock; 4Duke University Medical Center, Durham, North Carolina; 5Oregon Health Sciences University, Portland; 6Massachusetts General Hospital, Harvard Medical School, Boston; 7University of Iowa Health Care, Iowa City; 8Fred Hutchinson Cancer Research Center, Seattle, Washington; and 9EpiSpectrum, Markham, Canada

Figure 1. Frequency of invasive fungal infections from 2004 through 2006, as reported by the Prospective Antifungal Therapy Alliance participating centers for hematopoietic stem cell transplant recipients (results are presented as the absolute number of invasive fungal infections reported during each calendar year). Data from 2003 and 2007 are not presented, because reporting might not have been optimal during 2003, which was the first year of enrollment, and for 2007, a lag between patient identification, reporting, and completion of each case might have limited the number of presented cases. IA, invasive aspergillosis; IC, invasive candidiasis.
References


