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Clinical epidemiology of 960 patients with invasive aspergillosis from the PATH Alliance registry

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Summary *Objectives:* The study investigated the epidemiology and outcome of invasive aspergillosis (IA), an important cause of morbidity and mortality in immunocompromised patients.
Methods: Cases of proven/probable IA from the Prospective Antifungal Therapy Alliance (PATH Alliance®) registry — a prospective surveillance network comprising 25 centers in the United States and Canada that collected data on invasive fungal infections from 2004 to 2008 — were analyzed with respect to clinical outcome.
Results: Nine hundred and sixty patients with IA were enrolled, the most frequent underlying disease being hematologic malignancy ($n = 464$ [48.3%]). Two hundred and eighty patients (29.2%) received solid organ transplant; 268 patients (27.9%) underwent hematopoietic stem cell transplantation. Identified isolates included *Aspergillus fumigatus* (72.6%), *Aspergillus flavus* (9.9%), *Aspergillus niger* (8.7%) and *Aspergillus terreus* (4.3%). The lung was most frequently affected. Following diagnosis, 47% patients received monotherapy — voriconazole (70%), an amphotericin B formulation (13.8%), or an echinocandin (10.5%) — while 279 patients (29%) received combination therapy. Twelve-week overall survival was 64.4%.
Conclusions: In this series of patients with IA, the lung was the predominant focus of infection, *A. fumigatus* was the major species isolated, and overall survival appeared slightly improved compared with previous reports.

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Introduction

Invasive aspergillosis (IA) is a major cause of morbidity and mortality in immunocompromised patients and its diagnosis, prevention, and treatment comprise daunting tasks for clinicians. Risk factors for developing IA have been thoroughly studied, but despite its incidence and severity there remains a lack of information on the contemporary epidemiology of IA. This knowledge gap threatens to impede development of future advances against IA, limiting our understanding of pathogenesis and optimal treatment strategies. Several previous sizeable collections of patients with IA[1–4] helped shape our earlier understanding of the epidemiologic landscape of IA, but they suffer the limitations of any non-contemporary analysis. A larger, more contemporary and prospective, multicenter study of IA exclusively in transplant recipients illustrated subpopulation-specific current risk factors, but did not provide a complete epidemiologic picture.[5]

The epidemiology of IA is changing due to modern medical advances against classic underlying diseases, newer risk groups developing, emerging antifungal strategies, evolving antifungal resistance, and novel molecular diagnostic tools.[6] It is therefore difficult to extrapolate current prognostic and treatment recommendations from outdated epidemiologic information. In this study, we evaluate the more contemporary epidemiology, infection characteristics, and outcomes of IA using the Prospective Antifungal Therapy Alliance (PATH Alliance®) registry, a prospective, multicenter observational registry that collects clinical data on patients with invasive fungal infections.

A prospective surveillance network such as this has the ability to augment our clinical knowledge. While randomized clinical trials (RCTs) remain the gold standard in clinical medicine for defining optimal therapies, registries have different strengths. Registries such as the PATH Alliance that gather information over a period of time have the potential to highlight significant trends in diagnostic and treatment practices, and in the epidemiology of a broader population of patients.[7–14]

Methods

Study design and data collection

The PATH Alliance registry is an invasive fungal infection surveillance network comprised of 25 medical centers in the United States (US) and Canada, using methodology previously described in detail.[12] Investigators at major medical centers in the US and Canada with large numbers of invasive fungal infections were asked to participate. Prospective surveillance was conducted to identify patients with an invasive fungal infection diagnosed between July 1, 2004 and September 30, 2008. Briefly, investigators reviewed laboratory and clinical data to identify patients with invasive fungal infections. Data were collected using a detailed web-interface data entry system with a uniform evaluation protocol used for diagnosis and outcome, including specific prompts to accurately define the correct diagnosis, designed to exclude patients that lacked true disease. All data entered were audited prior to study closure. Outcomes were recorded at 12 weeks after diagnosis or until death or loss to follow-up, and the data collection was extended to permit 12-week follow-up for all patients. Information collected included baseline demographic characteristics, underlying disease, type of transplant, use of corticosteroid and immunosuppressive therapy, absolute neutrophil count (ANC), infecting *Aspergillus* species, site of infection, antifungal and adjunctive therapies, and other comorbidities. Institutional review boards approved the study at each participating center. *Aspergillus* cultures and histological specimens were documented at each participating institution.

Definitions

Proven and probable IA was defined according to the consensus definitions of the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group.[15] Patients were only included if they met the definition of proven or probable IA. *Aspergillus* antigenemia in patients with relevant clinical signs and symptoms was determined by most investigating centers using the serum galactomannan ELISA assay (Bio-Rad, Hercules, CA), with IA defined according to the revised diagnostic criteria.[16] Galactomannan cut-off was determined by each center (optical density index of 0.5 or 1.0). Causative *Aspergillus* spp. was documented, when available; neutropenia was defined as an ANC of <500 cells/mm^3 at the day of diagnosis. The presence or absence of graft-versus-host disease (GVHD) was recorded, as well as the grade, if available. Corticosteroid and immunosuppressive therapy was defined as any use in the 30 days prior to diagnosis. Prior antifungal therapy was considered as any systemic antifungal therapy within 30 days prior to the diagnosis of IA. The day the clinical diagnosis was made was designated as Day 1. Primary antifungal therapy was defined as the antifungal treatment administered on Day 3 following diagnosis. This methodology was used so as to best define the true treatment each investigator intended and adequately allow for any unintended initial short-term therapy (e.g. weekend).

Statistical analyses

Descriptive analysis was used for baseline characteristics and subgroup analysis. Descriptive survival analysis was performed based on the whole patient group and for subpopulations. The survival distribution function was estimated using the Kaplan–Meier method; patients lost to follow-up prior to 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 Inc. Carey, NC).

Results

Baseline patient characteristics

Altogether, 960 patients diagnosed with proven or probable IA were enrolled during the 51-month period (Table 1). The

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Table 1 Patient baseline characteristics.

Patient characteristics	No. of Patients	%
Age, mean years (range)	51.5 (0—93)	—
n (%) <18	35	3.6
n (%) ≥18 and ≤65	763	79.5
n (%) >65	162	16.9
Sex		
Male	565	58.9
Ethnicity		
Caucasian	772	80.4
African American	74	7.7
Hispanic or Latino	42	4.4
Asian	27	2.8
American Indian or Alaska Native	5	0.5
Other	2	0.2
Unknown	38	4.0
Underlying disease[a]		
Hematologic malignancy	464	48.3
Solid organ transplant	280	29.2
Hematopoietic stem cell transplant	268	27.9
Solid tumor	53	5.5
HIV/AIDS	14	1.5
Inherited immunodeficiency disorder	4	0.4
Other[b]	22	2.3
Immunologic risk[a]		
ANC <500 cells/mm^3	324	33.8
Corticosteroid therapy	708	73.8
Immunosuppressive therapy	468	48.8
Type of hematologic malignancy[a]	268	
Acute myelogenous leukemia	144	31.0
Non-Hodgkin's lymphoma	79	17.0
Multiple myeloma	79	17.0
Acute lymphocytic leukemia	56	12.1
Myelodysplastic syndrome	45	9.7
Chronic lymphocytic leukemia	33	7.1
Hodgkin's lymphoma	21	4.5
Chronic myelogenous leukemia	16	3.5
Aplastic anemia	10	2.2
Other	17	3.7
Type of hematopoietic stem cell transplant		
Allogeneic: HLA-matched related	86	32.1
Allogeneic: HLA-matched unrelated	66	24.6
Allogeneic: haploidentical	13	4.9
Allogeneic: HLA mismatched	30	11.2
Autologous	73	27.2
Type of solid organ transplant[a]		
Lung	185	66.1
Kidney	40	14.3
Liver	39	13.9
Heart	22	7.9
Pancreas	14	5.0
Small bowel	13	4.6
Heart and lung	2	0.7

ANC = absolute neutrophil count; and HLA = human leukocyte antigen.

[a] Not mutually exclusive; patients could have >1 characteristics within a category.

[b] Contains non-transplant surgery and neonatal intensive care (NICU).

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mean age was 51.5 years (range 0–93 years), and the majority of the patients were male (58.9%) or Caucasian (80.4%). The most frequent underlying disease was hematologic malignancy ($n = 464$ [48.3%]), with acute myelogenous leukemia (AML), non-Hodgkin's lymphoma, and multiple myeloma being the most common hematologic malignancies. Approximately one-quarter of the patients with IA were solid organ transplant (SOT) recipients ($n = 280$ [29.2%]), most commonly lung transplant patients. A total of 268 patients (27.9%) had received a hematopoietic stem cell transplant (HSCT) and the majority of those (72.8%) were from allogeneic donors, largely HLA-matched related or unrelated donors. The median day post-HSCT that IA was diagnosed in 266 of these patients was 97 days. The incidence of IA could not be calculated for the specific subpopulations, as the number of patients with each underlying disease was not collected. At the date of diagnosis, 324 patients were neutropenic (33.8%), including 262 patients (27.3%) who were severely neutropenic (ANC <100 cells/mm^3). Corticosteroid therapy ($n = 708$ [73.8%]) or other immunosuppressive therapy ($n = 468$ [48.8%]) was commonly administered within the 30 days prior to IA diagnosis.

Aspergillosis epidemiology

The 960 patients with IA included 361 (37.6%) patients with proven IA and 599 (62.4%) patients with probable IA. There was a mean of 38.4 (range, 2–213; median, 25; interquartile range, 12–49) patients enrolled at each center (Table 2), with no disproportionate species distribution for any center (data not shown). A total of 748 *Aspergillus* isolates were identified by culture (Table 3), with an additional 251 (25.1%) patients diagnosed by galactomannan assays and/or biopsy results without growth of *Aspergillus*. The percentage of patients with a positive galactomannan assay ranged from 0.0 to 86.4% between different centers. In patients with a probable diagnosis of IA, the most frequently performed single diagnostic test was culture ($n = 177$ [29.6%]) followed by galactomannan assay ($n = 84$ [14.0%]) and biopsy ($n = 8$ [1.3%]). A combination of these tests was performed in 326 (54.4%) patients, while no diagnostic test was recorded in four (0.7%) patients. However, as the categorization of probable versus proven IA was obtained at database enrollment, some probable cases may have progressed to proven cases during the clinical course. Of the *Aspergillus* species identified, the majority of isolates were identified as *Aspergillus fumigatus* (72.6%), while other isolated major species included *Aspergillus flavus* (9.9%), *Aspergillus niger* (8.7%) and *Aspergillus terreus* (4.3%). In 37 patients, two different species were isolated; three separate species were isolated from one patient.

There was no significant difference in species distribution of the three major *Aspergillus* species in the three age groups (<18, 18–65, and >65 years) (Table 4). Similarly, there was no difference seen with *Aspergillus* species distribution across either neutropenia (ANC <500 cells/mm^3), severe neutropenia (ANC <100 cells/mm^3), or specific immunosuppressive agent use. While *A. fumigatus* was the predominant infecting species in every underlying

Table 2 Number of patients enrolled by center.

Center #	Center name	Patients
	Total	960
1	Hamilton Health Sciences[a]	2
2	Washington Hospital Center[a]	6
3	University of Pennsylvania[a]	6
4	Thomas Jefferson University Hospital[a]	7
5	Children's Memorial Hospital	8
6	University of Iowa	11
7	City of Hope National Medical Center	13
8	Mount Sinai School of Medicine	15
9	University of Alabama at Birmingham	16
10	Johns Hopkins Hospital[a]	17
11	MD Anderson — Infectious Diseases	19
12	University of Michigan	23
13	Emory University	26
14	University of Nebraska	28
15	University of Minnesota	41
16	Oregon Health & Science University	42
17	Hôpital Maisonneuve — Rosemont	44
18	MD Anderson — Hematologic Malignancy	48
19	Massachusetts General Hospital	50
20	Duke University	53
21	University of Wisconsin	56
22	University of Arkansas	89
23	University of Pittsburgh[a]	127
24	University of Washington	213
25	University of Miami	—

[a] Centers which did not use serum galactomannan ELISA assay for diagnosis of IA.

Table 3 Infecting *Aspergillus* spp.

Species	Number of isolates[a]	% of identified isolates
A. fumigatus[b]	543	72.6
A. flavus	74	9.9
A. niger	65	8.7
A. terreus	32	4.3
A. versicolor	23	3.1
A. ustus	6	0.8
A. nidulans	3	0.4
A. glaucus	2	0.3
Unspecified[c]	251	
Total	999	

[a] Patients could have more than one species.
[b] Includes two isolated teleomorphs.
[c] Includes patients with probable IA diagnosed by biopsy and /or galactomannan assays.

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Table 4 *Aspergillus* spp. distribution by patient.

Patient category	*A. fumigatus* ($n = 512$)	%	*A. flavus* ($n = 58$)	%	*A. niger* ($n = 48$)	%	Other ($n = 55$)	%	Multiple spp. ($n = 38$)	%	Unspecified spp. ($n = 249$)	%	Total ($n = 960$)	%
Hematologic malignancy	171	33.4	35	60.3	15	31.3	22	40.0	10	26.3	211	84.7	464	48.3
AML + ALL	67	39.2	17	48.6	9	60.0	15	68.2	2	20.0	90	42.7	200	43.1
Other	104	60.8	18	51.4	6	40.0	7	31.8	8	80.0	121	57.3	264	56.9
HSCT	99	19.3	13	22.4	8	16.7	8	14.5	6	15.8	134	53.8	268	27.9
Allogeneic HSCT	78	78.8	9	69.2	8	100.0	7	87.5	5	83.3	88	65.7	195	72.8
Autologous HSCT	21	21.2	4	30.8		0.0	1	12.5	1	16.7	46	34.3	73	27.2
Solid organ transplant	181	35.4	15	25.9	18	37.5	21	38.2	21	55.3	24	9.6	280	29.2
Lung	125	69.1	8	53.3	13	72.2	16	76.2	16	76.2	7	29.2	185	66.1
Other	56	30.9	7	46.7	5	27.8	5	23.8	5	23.8	17	70.8	95	33.9
Solid tumor	35	6.8	3	5.2	4	8.3	4	7.3	1	2.6	6	2.4	53	5.5
HIV/AIDS	11	2.1	2	3.4		0.0	1	1.8		0.0		0.0	14	1.5
Inherited immunodeficiency	2	0.4		0.0	1	2.1		0.0	1	2.6		0.0	4	0.4
Neutropenia														
ANC <100	80	15.6	18	31.0	8	16.7	15	27.3		0.0	141	56.6	262	27.3
ANC <500[a]	108	21.1	23	39.7	10	20.8	18	32.7	3	7.9	162	65.1	324	33.8
Age group (y)														
<18	19	3.7	2	3.4	3	6.3	3	5.5		0.0	8	3.2	35	3.6
18–65	402	78.5	45	77.6	36	75.0	46	83.6	32	84.2	202	81.1	763	79.5
>65	91	17.8	11	19.0	9	18.8	6	10.9	6	15.8	39	15.7	162	16.9
Immunosuppression	406	79.3	45	77.6	35	72.9	44	80.0	36	94.7	194	77.9	760	79.2
Corticosteroids only	147	36.2	18	40.0	10	28.6	18	40.9	11	30.6	90	46.4	294	38.7

Abbreviations: ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia; ANC, absolute neutrophil count; and HSCT, hematopoietic stem cell transplant.
[a] Includes ANC < 100.

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disease group, 60.3% of all the *A. flavus* isolates identified were implicated in infection in patients with hematologic malignancies. This disproportionate amount of *A. flavus* was similar in patients with AML or acute lymphocytic leukemia (ALL) versus all other hematologic malignancies. In all other underlying categories, the infecting species were distributed proportionally.

Clinical presentation

The lung was the most frequent site of infection, with 730 (76.0%) patients having IA lung infection only (Fig. 1). A total of 96 patients (10.0%) had evidence of infection in more than one anatomic site, but 81 of those also included infection of the lungs. Exclusive infection to a single site other than the lungs included the tracheobronchial tree ($n = 35$ patients), sinuses ($n = 30$), skin/soft tissue ($n = 27$), central nervous system ($n = 5$), and other miscellaneous sites ($n = 37$), which included bone, heart, and eyes. *A. fumigatus* was the most common species isolated from each infection site (Table 5), and the most commonly infected site with each individual *Aspergillus* species was the lung. While *A. fumigatus*, *A. flavus*, and *A. niger* were each distributed with approximately 60–80% infecting the lungs, *A. terreus* disproportionately infected the lungs (93.9%, 31/33).

Antifungal therapy

Primary antifungal therapy was judged to be that used on Day 3 following the diagnosis of proven or probable IA, to allow adequate time for the clinicians to implement their desired primary therapy after any initial delays or treatment modifications (e.g. weekend). A total of 728 (75.8%) patients were receiving antifungal therapy on Day 3 following diagnosis of IA; 449 of 728 patients (61.7%) were receiving antifungal monotherapy, most commonly with voriconazole ($n = 315$), an amphotericin B formulation ($n = 48$), or an echinocandin ($n = 33$; Table 6). Use of more than one concurrent agent was noted in 279 of 728 patients (38.3%) at Day 3 following diagnosis. The most common antifungal combination was voriconazole plus an echinocandin ($n = 161$), followed by voriconazole plus an amphotericin B formulation ($n = 42$), or an echinocandin plus an amphotericin B formulation ($n = 31$). A total of 348 occurrences of combination therapy comprising 56 unique combinations were recorded throughout the entire 12-week study period.

A total of 98.4% (945/960) of patients received some antifungal therapy during the course of IA. However, on Day 3 following diagnosis, 139 patients had missing data or were lost to follow-up (this ranged from 0 to 55% among different participating centers), and 27 had died by Day 3. Sixty-two (6.5%) patients were receiving no antifungal therapy and 18 (3.8%) were receiving therapy with no anti-*Aspergillus* activity (fluconazole) on Day 3. When the complete follow-up period was analyzed, it was noted that 15 patients had not received any appropriate therapy for IA during their entire disease course; of these, 10 patients died within 7 days, three more patients in the second week; one more each died on Day 17 and Day 72.

Throughout the full 12-week study period, voriconazole was the most commonly employed antifungal, with drug exposure in 723 patients (75.3%; Table 7). Other frequently used antifungal agents throughout the 12-week study period included caspofungin ($n = 287$, 29.9%), liposomal amphotericin B ($n = 199$, 20.7%), micafungin ($n = 139$, 14.5%), amphotericin B lipid complex ($n = 83$, 8.6%), and posaconazole ($n = 71$, 7.4%).

Mortality

Overall 12-week post-diagnosis Kaplan–Meier survival among these 960 patients with IA was 64.4% (Fig. 2). A total of 145 (15.1%) patients were censored due to loss to follow-up. The outcomes for patients diagnosed with either proven or probable IA due to *A. fumigatus* were similar except for the survival for patients with probable diagnosis of non-*fumigatus Aspergillus*, who displayed a numerically but not statistically significantly lower survival (Fig. 3). Overall 90-day Kaplan–Meier survival among patients with proven IA was 65.3%, while survival among the patients with probable IA was 63.9%. Of the three major identified *Aspergillus* spp. (Fig. 4), survival outcome was better with *A. niger* infection (79.9%), compared to infection with *A. fumigatus* (66.0%) and *A. flavus* (60.5%) or the other identified

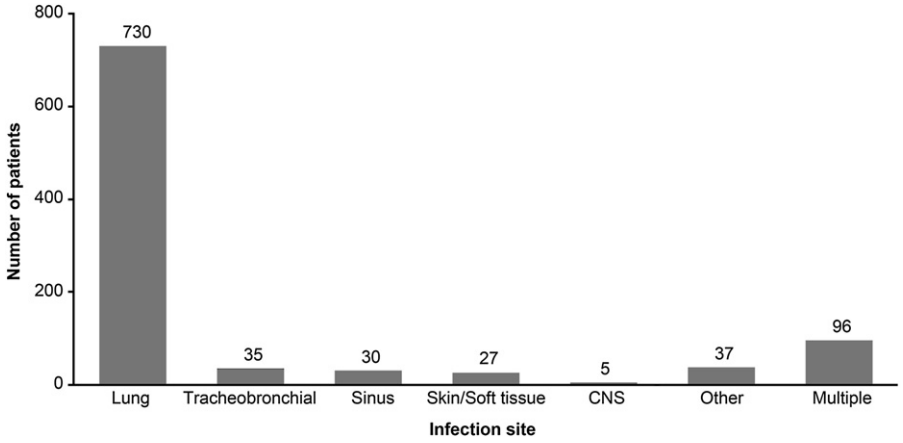

Figure 1 Invasive aspergillosis patients: breakdown by infection site.

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Table 5 Infection site by *Aspergillus* spp.

Infection site	*A. fumigatus*	*A. flavus*	*A. niger*	*A. terreus*	Other[a]	Unspecified	Total
Lung	466	46	56	31	23	222	867
Tracheobronchial	39	6	2	1	3	3	57
Sinus	18	11	3	1	2	10	47
Skin and soft tissue	18	7	4		3	5	40
Central nervous system	19	1	2			1	23
Blood	4	1	1			15	21
Abdominal	9	3	1			5	18
Skeleton	11	3				2	16
Heart	6		1			7	14
Orbital	2	1			1		5
Endophthalmitis	1						1
Other	3	1			2		8
Total	596	80	70	33	34	270	1117

[a] Includes *A. versicolor* (23), *A. ustus* (6), *A. nidulans* (3), *A. glaucus* (2).

Aspergillus spp. (60.2%). Infection with unspecified *Aspergillus* spp. (84.8%) (Table 4) mostly involved patients with hematologic malignancy or HSCT recipients, and was associated with worse survival (57.1%) (Fig. 4, "Unspecified *Aspergillus* spp."). In addition, patients with neutropenia at the day of diagnosis had a worse survival (56.6%) than those patients receiving other immunosuppressive therapy (68.0%).

In the four major subpopulations of patients (Fig. 5), overall Kaplan–Meier survival at 12 weeks post-diagnosis was greater in the SOT recipients (77.9%) compared with survival in patients with hematologic malignancy (59.6%), solid tumor (60.5%), or those undergoing HSCT (62.4%). Survival rates of allogeneic HSCT recipients (Table 4) and autologous HSCT recipients (Table 4) with IA were 59.7% and 71.3%, respectively.

Table 6 Primary antifungal therapy on Day 3.

Antifungal treatment	No. of patients	% Subgroup	% Group
Monotherapy	449	100.0	47.8
Voriconazole	315	70.2	
Liposomal amphotericin B	48	10.7	
Caspofungin	33	7.3	
Posaconazole	13	2.9	
Micafungin	12	2.7	
Amphotericin B lipid complex	11	2.45	
Itraconazole	10	2.2	
Amphotericin B deoxycholate	2	0.4	
Anidulafungin	2	0.4	
Blinded	2	0.4	
Amphotericin B colloidal dispersion	1	0.2	
Combination therapy	279	100.0	29.1
Voriconazole + echinocandin	161	57.7	
Voriconazole + amphotericin B	42	15.0	
Echinocandin + amphotericin B	31	11.1	
Other	45	16.1	
No therapy[a]	232	—	24.2

[a] Includes 207 cases with no treatment and 25 cases of fluconazole only on Day 3.

Table 7 Antifungal therapy throughout 12-week study period.

Antifungal	No. of patients[a]	%
Total patients	960	100
Voriconazole	723	75.3
Caspofungin	287	29.9
Liposomal amphotericin B	199	20.7
Micafungin	139	14.5
Amphotericin B lipid complex	83	8.6
Posaconazole	71	7.4
Fluconazole	68	7.1
Itraconazole	31	3.2
Amphotericin B deoxycholate	26	2.7
Anidulafungin	5	0.5
5-Fluorocytosine	3	0.3
Amphotericin B colloidal dispersion	3	0.3
Blinded	3	0.3
No treatment record[b]	96	10.0

[a] Treatment not mutually exclusive; multiple counts allowed.
[b] Fifty-two patients had incomplete data. For the remaining 44 patients with complete records, 29 had died by the date of diagnosis (Day 1), 10 more died within 7 days, 3 more in the second week; one more each died on day 17 and day 72.

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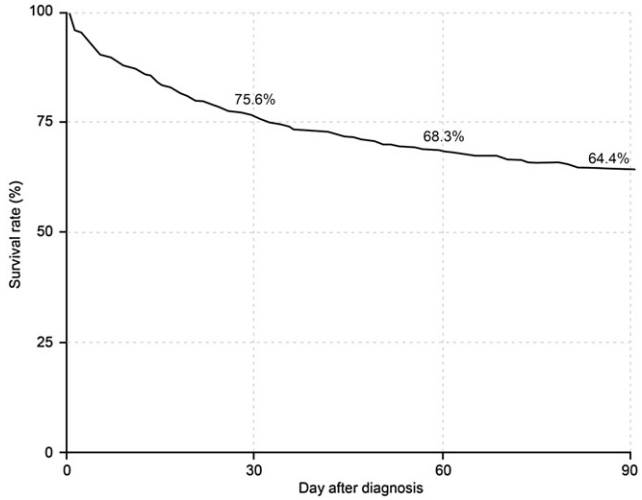

Figure 2 Overall survival for 960 patients with invasive aspergillosis (of whom 145 were lost to follow-up).

Discussion

This is the largest prospective multicenter analysis of contemporary IA reported to date, adding to previous reports from the PATH Alliance database.[7,8] As seen in other large studies, the most common underlying disease in patients with IA was hematologic malignancy (48.3%), particularly AML, non-Hodgkin's lymphoma, multiple myeloma, and ALL. We found that 53.7% (144/268) of hematologic malignancy patients with IA had AML and 12.1% (56/268) had ALL — both slightly fewer than in a large Italian study of patients with hematologic malignancy, which reported that 69% (213/310) of IA occurred in patients with AML and 14% in patients with ALL.[17] The overall 12-week survival in the 464 patients in our study with hematologic malignancy was 59.6%, leading to the worst survival of the major underlying conditions. Consistent with previously published reports,[18–21] the majority of our HSCT recipients with IA received allogeneic grafts (72.8% of the group) rather than autologous transplants. Likewise, the median day post-HSCT that IA was diagnosed in 266 of these patients was 97 days, similar to the median of 99 days found in the TRANSNET surveillance report of 425 cases of IA from 23 US transplant centers.[19]

Our distribution showing lung transplant recipients to have the greatest number of cases of IA (66.1%) exceeds the 44% of TRANSNET lung transplant recipients, but we found lower rates of reported disease in kidney (14.3%) and liver (13.9%) transplant patients. Notably, TRANSNET found a higher number of cases of IA in heart transplant recipients (23%) than in our study (7.9%).[22]

The most common species identified in our survey was *A. fumigatus* (72.6%), followed by *A. flavus* (9.9%), *A. niger* (8.7%) and *A. terreus* (4.3%). While some studies have reported a similar distribution,[20,23,24] other analyses have suggested a recent trend toward more frequent infection with species other than *A. fumigatus*,[18] with a specific increase in *A. flavus* and *A. terreus*.[25] However, the distribution of *Aspergillus* spp. in our study was consistent with the previous Mycoses Study Group *Aspergillus* culture study, which found *A. fumigatus* (67%) to be the most common species causing invasive disease, followed by *A. flavus* (16%), *A. niger* (5%), *A. terreus* (3%), and *A. nidulans* (1%).[26] Consistent with our study, other earlier epidemiologic studies also found that *A. fumigatus* was the most common species (66%) identified in a multicenter cohort,[1] a large single-center review (67%),[18] a multinational

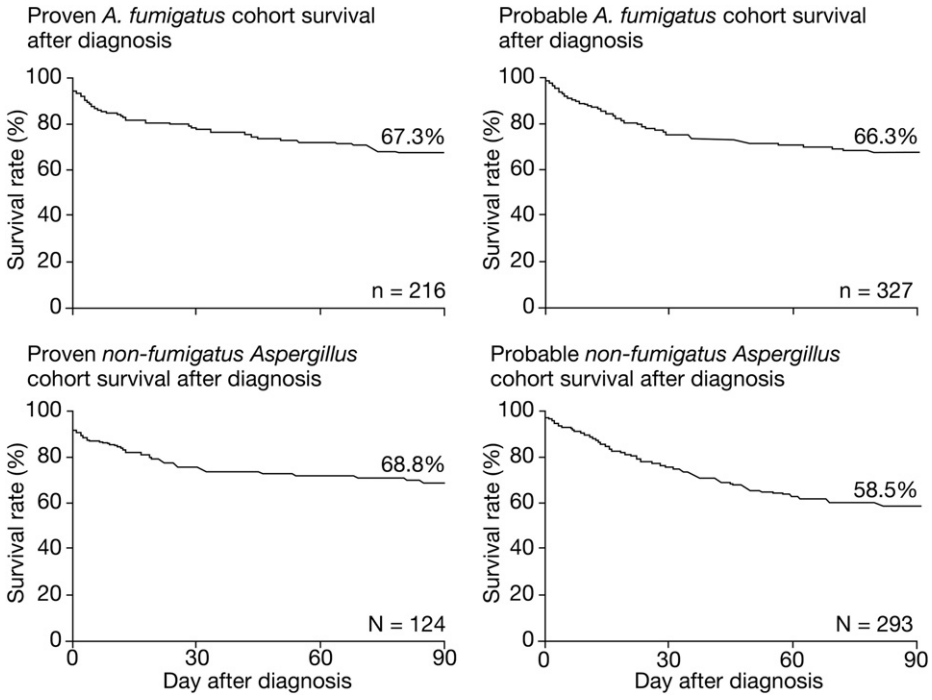

Figure 3 Overall survival by *Aspergillus* spp. diagnostic category.

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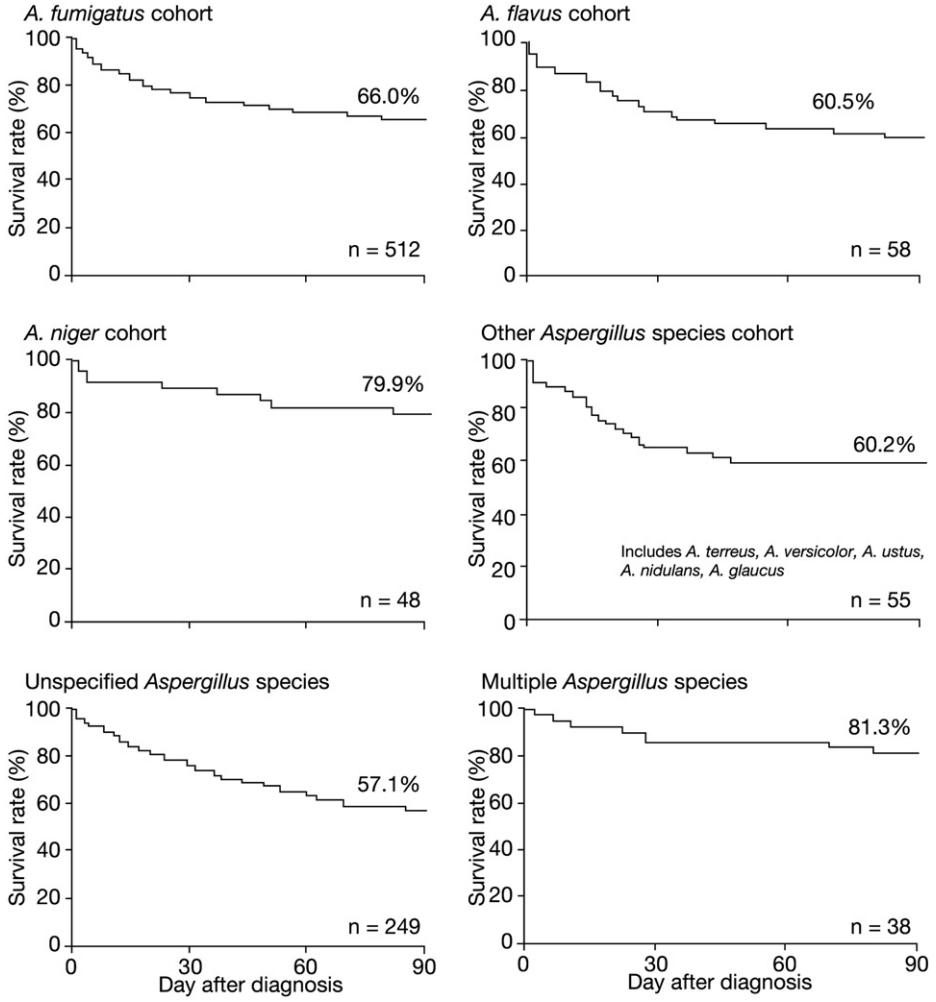

Figure 4 Overall survival by *Aspergillus* spp.

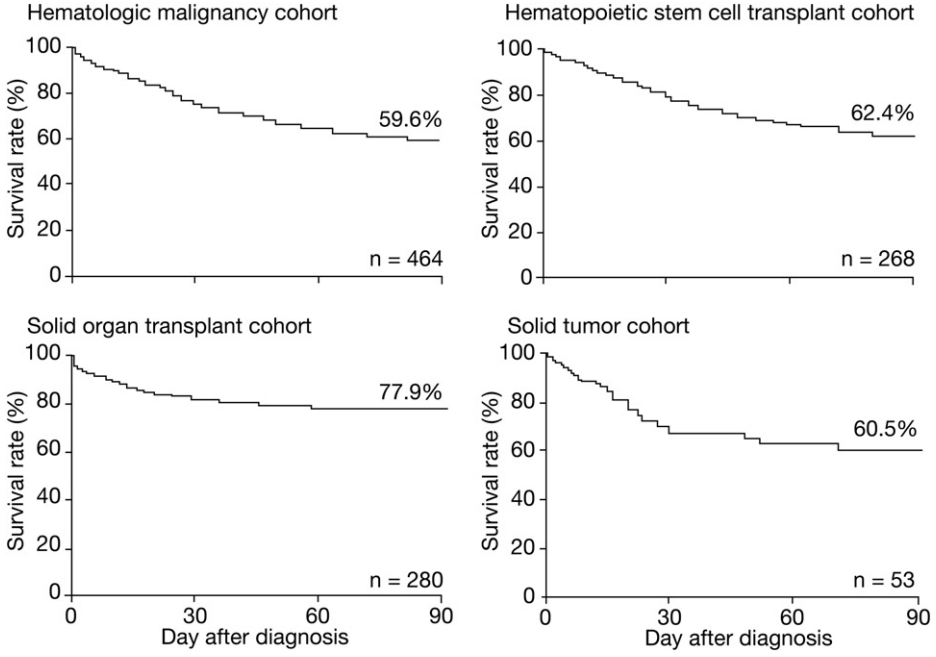

Figure 5 Overall survival by patient underlying condition.

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antifungal trial (71%),[2] the TRANSNET multicenter network (59.1%),[19] and a recent multicenter French study (79.7%).[27]

Several previous studies have shown that infection with *A. terreus* was associated with worse outcomes compared to that with *A. fumigatus*.[28,29] In one series, neutropenia at diagnosis was also more commonly seen in patients infected with *A. terreus*,[28] and in another series dissemination was more commonly seen following *A. terreus* infection.[29] Contrary to the findings in these smaller studies, we did not find a correlation with neutropenia and the infecting *Aspergillus* spp.

Survival outcomes appeared better in patients who developed infection with *A. niger* compared with other *Aspergillus* spp. Our study appears to be the first epidemiologic study to analyze survival based on individual *Aspergillus* spp., as other large studies do not separate outcomes in this way.[5,17,19,27] *A. niger* is an uncommon pathogen in the immunocompromised host. In the largest *Aspergillus* culture study, *A. niger* had the lowest rate of invasive disease (36%) compared with the other *Aspergillus* spp. The previous largest report of *A. niger* infection in patients with hematologic malignancy summarized only eight cases; yet seven of those patients died, and death was attributable to progressive *A. niger* infection in six of them.[30] In addition, infection in the 37 patients with multiple identified *Aspergillus* spp. was associated with greater overall survival (81.3%), but this could be related to respiratory tract colonization and not true infection with multiple species.

Three-quarters of the patients in this study were receiving appropriate therapy for IA by Day 3 following diagnosis; however, that leaves a worrisome number of patients with no effective treatment immediately following diagnosis. Over half of the patients received voriconazole either as monotherapy (70% of monotherapy treatments) or in combination with an echinocandin (58% of combination treatments) or amphotericin B (15% of combination treatments). This is similar to the recent French survey[27] in which 80% of patients received antifungal monotherapy, most commonly with voriconazole, and approximately 20% received combination antifungal therapy, most commonly with voriconazole and caspofungin. In our study, 29% of patients received primary combination therapy, which was slightly higher than the 16% reported in an Italian multicenter analysis.[31]

In this study 12-week survival rates ranged from 59.6% (hematologic malignancy), 60.5% (solid tumors) and 62.4% (HSCT), to 77.9% (SOT); however, nearly 15% of the patients were lost to follow-up. Overall mortality, after the diagnosis of IA, was historically high: one study reported that 78% of patients who developed IA after allogeneic HSCT died by12 weeks or the end of therapy.[20] The TRANSNET study reported 12-week all-cause mortality rates of 57.5%[5] and a 1-year mortality of 74.6% among HSCT recipients.[19] Other studies have shown that overall survival after the diagnosis of IA has improved in recent years, especially among specific cohorts of patients with hematologic malignancies and in allogeneic HSCT recipients, with outcomes dependent on specific host variables.[32,33] Our data appear consistent with these improved overall outcomes, although there appears to be room for improvement, especially among patients with hematologic malignancies.

This study has several limitations, primarily related to the lack of information on the total number of patients at risk in each category needed to calculate the incidence of infection or risk factors for developing infection within each patient subgroup. Similarly, although investigators at each site were instructed to enroll into the registry all consecutively identified patients with invasive fungal infections, there was variability in the screening process at each center. In addition, one center contributed 22% of cases while another contributed <1% (range, 2–213 patients per site; Table 2). It was not possible to determine if there was complete capture of cases in high-enrolling centers. Although galactomannan assay from bronchoalveolar lavage was not performed for diagnosis of IA, many centers now use galactomannan assays for this purpose. Recent multicenter studies of IA did not report individual site enrollment, so it is unclear how our results compare.[5,19]. Few children with IA were enrolled in this study due to the limited inclusion of dedicated children's hospitals, and this limits comparisons with other pediatric reports. Cases were diagnosed from 2004 to 2008, but due to site start-up the majority of cases were diagnosed in the later years of the study (data not shown). However, additional IA strategies have developed since 2004 — including bronchoalveolar lavage galactomannan and the increased use of posaconazole and combination antifungal therapy — that may not have been fully captured in this database. Additionally, a delay in initiation of therapy was observed for some patients, but the reasons for this delay were not captured by the registry. We did not know when cultures or other diagnostic tests were actually reported to physicians and this may have accounted for delays in initiation of therapy. In addition, it is unknown if patient data was entered simultaneously into both PATH Alliance and TRANSNET registries. Finally, information about surveillance methods, supportive care strategies, or the distinction between prophylactic, pre-emptive and empirical antifungal therapy is often difficult to accurately discern.

Despite these limitations, meaningful observations were made from this analysis. First, there is a striking variation in the types of patient in whom IA is diagnosed in the US and Canada. In this analysis, *A. fumigatus* remains the most common causative species, although other species continue to cause disease, with variable rates in each host category. While *A. niger* is a less common organism in IA, outcomes with infection — even in the lungs — appear better than with other *Aspergillus* spp. Outcomes, observed as overall survival, appear improved compared with historical numbers generated in the 1990s, but are variable in host categories, with particular opportunities for improvement in patients with underlying malignancies. Future studies will be performed to identify host and therapeutic variables that dictate outcomes within specific cohorts of patients.

Role of the funding source

This data collection and analysis was supported by Astellas Pharma US.

Conflict of interest

William Steinbach's institution received a grant for PATH data collection from Astellas Pharma Global Development;

and he received consultancy fee/honoraria for consulting on the study design from Astellas Pharma. He is a member of the advisory board for Astellas and Merck, has received laboratory grants from Astellas and Merck, and is a member of the speakers' bureau for Pfizer.

Kieren Marr's institution received a grant for PATH data collection from Astellas Pharma Global Development. She also reports having received consultancy fee/honoraria for consulting on the study design from Astellas Pharma. Other consultancies are to Merck, Optimer, Novartis, and Pfizer, and grants from Pfizer, Merck, and Sigma Tau.

Elias Anaissie's institution received a grant for PATH data collection from Astellas Pharma Global Development; and he received consultancy fee/honoraria for consulting on the study design from Astellas Pharma. He is a consultant to Astellas on a vaccine protocol for cytomegalovirus infection.

Nkechi Azie, Shun-Ping Quan, and Ulf Meier-Kriesche are employees of Astellas Pharma.

Senu Apewokin's institution received a grant for PATH data collection from Astellas Pharma Global Development.

David Horn LLC has received a consultancy fee/honoraria from Astellas Pharma.

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