Epidemiology and Outcome of Invasive Fungal Infection in Adult Hematopoietic Stem Cell Transplant Recipients: Analysis of Multicenter Prospective Antifungal Therapy (PATH) Alliance Registry


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Background. With use of data from the Prospective Antifungal Therapy (PATH) Alliance registry, we performed this multicenter, prospective, observational study to assess the epidemiologic characters and outcomes of invasive fungal infection (IFI) in hematopoietic stem cell transplant (HSCT) recipients.

Methods. Sixteen medical centers from North America reported data on adult HSCT recipients with proven or probable IFI during the period July 2004 through September 2007. The distribution of IFIs and rates of survival at 6 and 12 weeks after diagnosis were studied. We used logistic regression models to determine risk factors associated with 6-week mortality for allogeneic HSCT recipients with invasive aspergillosis (IA).

Results. Two hundred thirty-four adult HSCT recipients with a total of 250 IFIs were included in this study. IA (59.2%) was the most frequent IFI, followed by invasive candidiasis (24.8%), zygomycosis (7.2%), and IFI due to other molds (6.8%). Voriconazole was the most frequently administered agent (68.4%); amphotericin B deoxycholate was administered to a few patients (2.1%). Ninety-three (46.7%) of 199 HSCT recipients with known outcome had died by week 12. The 6-week survival rate was significantly greater for patients with IA than for those with invasive candidiasis and for those with IFI due to the Zygomycetes or other molds ($P < .001$). The 6-week mortality rate for HSCT recipients with IA was 21.5%. At 6 weeks, there was a trend toward a worse outcome among allogeneic HSCT recipients with IA who received myeloablative conditioning ($P = .07$); absence of mechanical ventilation or/and hemodialysis ($P = .01$) were associated with improved survival.

Conclusions. IA remains the most commonly identified IFI among HSCT recipients, but rates of survival in persons with IA appear to have improved, compared with previously reported data. Invasive candidiasis and IFI due to molds other than *Aspergillus* species remain a significant problem in HSCT recipients.

Hematopoietic stem cell transplant (HSCT) recipients have a high risk of acquiring invasive fungal infection (IFI) by virtue of cytopenias and receipt of therapies to prevent and treat graft-versus-host disease. During the past 2 decades, the epidemiology of IFI has changed: fluconazole prophylaxis has been successfully used to prevent *Candida albicans* infection [1, 2], and mold infections have become more common [3, 4]. Changes in transplantation practices, including the sources used for stem cells, conditioning regimens, and strategies to diagnose and treat IFI, have likely impacted the epide-
demiology and outcomes of IFI. However, most recent data are limited to single-center studies [3–6].

The Prospective Antifungal Therapy (PATH) Alliance is a prospective, multicenter, observational registry that collects data and monitors trends in the epidemiologic characteristics, diagnosis, treatment, and outcomes of IFI in North America. We performed this multicenter, prospective, observational study to assess the epidemiology and outcomes of IFI in HSCT recipients.

**METHODS**

**Case identification and data collection.** The PATH Alliance consists of 23 medical centers in the United States and Canada. Data are entered prospectively into electronic case report forms with use of methods that have been described elsewhere [7]. This study was performed by review of data registered by 16 medical centers that reported at least 1 adult (age, ≥19 years) HSCT recipient with a proven or probable IFI during the period July 2004 through September 2007.

Variables collected included the subject’s demographic characteristics, underlying disease, transplant characteristics, type of IFI, and outcome. Underlying disease and transplant characteristics included data on the type and state of hematologic malignancy or other underlying disease, gastrointestinal tract mucositis, conditioning regimen, stem cell manipulation, history of prior HSCT, stem cell source, and presence and severity of graft-versus-host disease (defined as acute [grade II–IV] or chronic). In addition, information on the following immunologic risk factors was collected: absolute neutrophil count, receipt of total body irradiation, donor lymphocyte infusion, use of corticosteroids (within 30 days before the diagnosis), and use of other immunosuppressive agents. The following host data were collected: demographic characteristics, receipt of prior antifungal therapy (within 30 days before the diagnosis of IFI), organ function, organ support requirements, and concomitant viral or bacterial infection (within 30 and 7 days before the diagnosis of IFI, respectively). Detailed information pertaining to the IFI was collected, including the time after HSCT, fungal genus and species (when isolated), diagnostic modalities, site of infection, antifungal therapy history, and therapeutic procedures.

**Definitions.** IFIs were defined in accordance with published guidelines [8]. The day of diagnosis was defined as the day that the first positive culture or pathologic test result was provided to the treating physician. The outcome of IFI therapy was recorded at final assessment (i.e., 12 weeks after diagnosis of IFI) as complete or partial response, stable condition, worsening condition, or unknown, as assessed by investigators and as described elsewhere [7].

**Analyses.** The distribution of IFIs across the different types of HSCTs and crude mortality rates at weeks 6 and 12 are described. Survival analyses were performed on the basis of the type of the HSCT (allogeneic transplant from an unrelated or unmatched, related donor; or autologous transplant), the different IFIs (invasive candidiasis [IC], invasive aspergillosis [IA], or IFI due to the Zygomycetes or other molds), and type of conditioning regimen (myeloablative vs. nonmyeloablative; for allogeneic HSCT recipients only).

We used logistic regression analysis to determine the major risk factors associated with 6-week mortality for allogeneic HSCT recipients with IA, excluding patients who received cord blood transplants. Risk factors evaluated for IA-associated mortality included the following variables: age, HSCT type (allogeneic transplant from an unrelated or unmatched, related donor), stem cell source (peripheral blood vs. bone marrow), conditioning regimen (myeloablative vs. nonmyeloablative), organ support (dialysis dependence or and mechanical ventilation), cytomegalovirus infection, and disease risk (“high risk” was defined as acute or chronic lymphocytic leukemia, lymphoma, multiple myeloma, or acute myelogenic leukemia not in first remission; “low risk” was defined as all the rest of the hematologic malignancies). Different models were constructed on the basis of the interval between transplantation and diagnosis: one for early diagnosis of infection (≤40 days after transplantation) and the other for late diagnosis of infection (>40 days after transplantation). Because of the small number of patients, risk factor analysis for mortality was not performed for patients with IC or with IFI due to molds other than Aspergillus species.

Comparisons between categorical variables were performed by Fisher’s exact test or the χ² test; for continuous variables, Student’s t test or analysis of variance was used. Survival distribution function was estimated using the Kaplan-Meier product-limit method. Bivariate analyses and cluster analysis were used to screen for potential mortality risk factors from a list of clinically significant variables; the final mortality risk factors were then determined through stepwise logistic regression with a .1 significant level.

**RESULTS**

**Baseline patient characteristics.** Two hundred thirty-four adult HSCT recipients with a total of 250 proven or probable IFIs were included in this study. A total of 161 patients (68.8%) had received an allogeneic HSCT, and 73 (31.2%) had received an autologous HSCT. Among the allogeneic HSCT recipients, 63 (39.1%) patients had received an HLA-matched HSCT from a related donor, 59 (36.6%) had received an HLA-matched HSCT from an unrelated donor, 31 (19.3%) had received an HLA-mismatched HSCT, and 8 (5.0%) had received a haplo-identical HSCT. Sixteen medical centers contributed a median of 5.5 patients each (range, 2–93 patients). Of note, 147 HSCT...
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Detailed descriptions of the patients’ baseline characteristics, underlying disease, comorbidity, and HSCT specifics are presented in table 1. A significant number of autologous HSCT recipients were treated with corticosteroids (55 patients [75.3%]) and 2 patients (2.7%) in this group received other immunosuppressive agents. More than one-third (58 patients [36.0%]) of allogeneic HSCT recipients had acute (grade II–IV) or chronic graft-versus-host disease. Among the 161 allogeneic HSCT recipients, calcineurin inhibitors were the most commonly administered immunosuppressive agents (118 patients [73.3%]), followed by mycophenolate mofetil (53 patients [32.9%]), and sirolimus (9 patients [5.6%]).

IFI. The distribution of IFIs is outlined in table 2. IA was the most commonly observed IFI (148 [59.2%] of 250 cases), followed by IC (62 cases [24.8%]), zygomycosis (18 cases [7.2%]), and IFI due to other molds (17 cases [6.8%]). There were no notable differences in the distribution of IFIs across the different HSCT categories. The frequency of IFI, as reported by the participating centers of the PATH Alliance during 2004–2007, appeared to have changed over time. In contrast to cases of IA that remained relatively stable during 2005–2006, the frequency of IC has decreased, whereas that of IFI due to Zygomycetes and other molds appears to have increased (data not shown). Aspergillus fumigatus was the most frequently isolated Aspergillus species (55 [37.2%] of 148 cases), whereas the species were not identified in 78 cases (52.7%) of IA. The diagnosis of IA was proven in 17 cases (11.5%) and was considered probable in 131 cases (88.5%). The galactomannan assay (in the serum and/or bronchoalveolar lavage fluid specimens) was used for diagnosis of 108 cases (73.0%) of IA. The majority of cases of IC were due to non-albicans species of Candida (47 [75.8%] of 62 cases); Candida glabrata was the most frequently isolated species (27 [43.5%] of 62 cases), and 7 cases (11.3%) were due to Candida krusei.

The interval between HSCT and diagnosis of IFI was studied for patients with a single IFI (figure 2). The median time after HSCT was 77 days (range, 0–2219 days) for IC and 82 days (range, 3–6542 days) for IA. There was a trend for IC to occur earlier after transplantation in autologous HSCT recipients (median interval, 28 days; range, 6–1559 days) than in allogeneic HSCT recipients (median interval, 108 days; range, 0–2219 days; \(P = .11\)). In contrast, the interval between HSCT and IA diagnosis for autologous HSCT recipients (median, 51 days; range, 3–2065 days) and allogeneic HSCT recipients (median, 83 days; range, 3–6542 days) did not appear to differ significantly (\(P = .63\)). IFI due to Zygomycetes and other molds occurred late after HSCT (median interval, 173 days; range, 7–2254 days); it tended to occur later in autologous HSCT recipients (median interval, 412 days; range, 190–2254 days) than in allogeneic HSCT recipients (median interval, 162 days; range, 7–932 days; \(P = .21\)). When the interval between HSCT and IFI diagnosis was studied separately for the different allogeneic HSCT categories (matched, related donor vs. other), no major differences were observed (data not shown). Allogeneic HSCT recipients who received a myeloablative conditioning regimen were more likely to receive a diagnosis of IC early after HSCT (median interval, 65 days; range, 0–1594 days), compared with those who received a nonmyeloablative conditioning regimen (median interval, 590 days; range, 120–2219 days; \(P = .26\)). In contrast, no major differences in the interval between HSCT and diagnosis of IFI due to molds were observed between allogeneic HSCT recipients on the basis of their conditioning regimens (data not shown).

Antifungal therapy. Overall, voriconazole was the most frequently administered agent (160 patients [68.4%]), followed by caspofungin (115 patients [49.1%]) and the lipid formulations of amphotericin B (99 patients [42.3%]). Of note, amphotericin B deoxycholate was administered to few patients (5 patients [2.1%]). For IC, caspofungin was the most frequently administered agent (30 [52.6%] of 57 patients), followed by the lipid formulations of amphotericin B (20 patients [35.1%]) and fluconazole (18 patients [31.6%]). The vast majority of patients with IA (122 [84.7%] of 144 patients) and with IFI due to other molds (13 [76.5%] of 17 patients) received therapy with voriconazole. The lipid formulations of amphotericin B were more frequently administered in cases of zygomycosis (15 [83.3%] of 18 cases) (figure 3). Combination therapy, defined as concomitant administration of \(\geq 2\) antifungal agents, was most commonly used in cases of IA (68 [47.2%] of 144 patients), IFI due to other molds (9 patients [52.9%]), and zygomycosis (6 patients [33.3%]). Treatment with voriconazole plus the echinocandins was the most frequently used combination regimen for patients with IA (56 [82.4%] of 68 patients who received voriconazole combination therapy); voriconazole
Table 1. Baseline patient characteristics for 234 hematopoietic stem cell transplant (HSCT) recipients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Allogeneic transplant</th>
<th>Unrelated or unmatched, related donor</th>
<th>Autologous transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Matched, related donor (n = 63)</td>
<td>Related donor (n = 98)</td>
<td>(n = 73)</td>
</tr>
</tbody>
</table>

Demographic characteristic
- **Age, years**
  - Mean ± SE: 48.7 ± 1.73, 50.62 ± 1.41, 57.8 ± 1.3
  - Range: 19.5–74.3, 19.1–74.4, 23.8–76.9
- **Male sex**: 38 (60.3), 59 (60.2), 41 (56.2)
- **White ethnicity**: 54 (85.7), 62 (63.3), 62 (84.9)

Underlying disease
- **Acute leukemia**: 36 (57.1), 47 (48.0), 1 (1.4)
- **Chronic leukemia**: 7 (11.1), 14 (14.3), 1 (1.4)
- **Lymphoma**: 10 (15.9), 21 (21.4), 19 (26.0)
- **Multiple myeloma**: 4 (6.3), 5 (5.1), 50 (68.5)
- **Myelodysplastic syndrome**: 8 (12.7), 16 (16.3), 1 (1.4)
- **Other**: 3 (4.8), 3 (3.1), 4 (5.5)

Transplant characteristic
- **Stem cell source**
  - Bone marrow: 10 (15.9), 18 (18.4), 2 (2.7)
  - Peripheral blood: 53 (84.1), 70 (71.4), 70 (95.9)
- **Stem cell manipulation: T cell depletion**: 5 (7.9), 6 (6.1), 1 (1.4)
- **CD34 selected**: 6 (9.5), 6 (6.1), 3 (4.1)
- **Receipt of myeloablative conditioning**: 42 (66.7), 62 (63.3), 73 (100.0)
- **Prior HSCT**: 7 (11.1), 25 (25.5), 41 (56.2)

Organ function and transplantation complications
- **Dialysis dependence**: 2 (3.2), 7 (7.1), 10 (13.7)
- **Diabetes mellitus**: 26 (41.3), 48 (49.0), 16 (21.9)
- **Requirement of total parenteral nutrition**: 26 (41.3), 44 (44.9), 11 (15.1)
- **Mechanical ventilation**: 8 (12.7), 8 (8.2), 14 (19.2)
- **GVHD**
  - Acute (grade II–IV): 20 (31.7), 38 (38.8), 1 (1.4)
  - Chronic: 15 (23.8), 18 (18.4), 0 (0)
- **Mucositis (grade I–IV)**: 11 (17.5), 21 (21.4), 23 (31.5)
- **Cytomegalovirus infection**: 5 (7.9), 15 (15.3), 8 (11.0)
- **Bacterial infection**: 25 (39.7), 38 (38.8), 28 (38.4)

Immunologic risk factors
- **Absolute neutrophil count, <500 cells/mm³**: 28 (44.4), 57 (58.2), 51 (69.9)
- **Total body irradiation**: 8 (12.7), 26 (26.5), 4 (5.5)
- **Donor lymphocyte infusion**: 2 (3.2), 4 (4.1), 3 (4.1)
- **Receipt of corticosteroid therapy**: 49 (77.8), 69 (70.4), 55 (75.3)
- **Receipt of immunosuppressive therapy**: 45 (71.4), 87 (88.8), 2 (2.7)

**NOTE.** Data are no. (%). of patients, unless otherwise indicated. GVHD, graft-versus-host disease.

- Includes 59 recipients of HSCTs from HLA-matched, unrelated donors; 8 recipients of transplants from haploidentical donors; and 31 recipients of transplants from HLA-mismatched donors.
- Underlying disease, organ function, and immunologic risk factors were not mutually exclusive i.e., patients could have >1 factor.
- One recipient of an HSCT from a matched, related donor and 2 recipients of autologous HSCTs had a solid tumor, and 2 recipients of allogeneic HSCTs from unrelated donors had a surgical condition. The remaining patients had another hematologic condition.
- The stem cell source for 10 recipients of allogeneic HSCTs from unrelated donors was cord blood.
Table 2. Distribution of infecting fungal pathogens and species observed in 234 hematopoietic stem cell transplant (HSCT) recipients with a total of 250 invasive fungal infections (IFIs).

<table>
<thead>
<tr>
<th>IFI</th>
<th>Allogeneic transplant</th>
<th>Unrelated or unmatched, related donor</th>
<th>Autologous transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Matched, related donor</td>
<td>(n = 71)</td>
<td>(n = 102)</td>
</tr>
<tr>
<td>Candida species</td>
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<td></td>
</tr>
<tr>
<td>All</td>
<td>20 (28.2)</td>
<td>23 (22.5)</td>
<td>19 (24.7)</td>
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<tr>
<td>Candida albicans</td>
<td>5 (25.0)</td>
<td>4 (17.4)</td>
<td>6 (31.6)</td>
</tr>
<tr>
<td>Candida glabrata</td>
<td>7 (35.0)</td>
<td>13 (56.5)</td>
<td>7 (36.6)</td>
</tr>
<tr>
<td>Candida krusei</td>
<td>2 (10.0)</td>
<td>2 (8.7)</td>
<td>3 (15.8)</td>
</tr>
<tr>
<td>Candida parapsilosis</td>
<td>3 (30.0)</td>
<td>2 (8.7)</td>
<td>2 (10.5)</td>
</tr>
<tr>
<td>Candida tropicalis</td>
<td>3 (30.0)</td>
<td>1 (4.3)</td>
<td>1 (5.3)</td>
</tr>
<tr>
<td>Aspergillus species</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>38 (53.5)</td>
<td>61 (59.8)</td>
<td>49 (63.6)</td>
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<tr>
<td>Aspergillus flavus</td>
<td>2 (5.3)</td>
<td>1 (1.6)</td>
<td>2 (4.1)</td>
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<td>Aspergillus fumigatus</td>
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<td>27 (44.3)</td>
<td>12 (24.5)</td>
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<td>Aspergillus niger</td>
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<td>2 (3.3)</td>
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<td>Aspergillus terreus</td>
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<td>0 (0)</td>
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<tr>
<td>Other</td>
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<td>2 (3.3)</td>
<td>1 (2.0)</td>
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<tr>
<td>Unknown</td>
<td>16 (42.1)</td>
<td>29 (47.5)</td>
<td>33 (67.3)</td>
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<td>Zygomycetes</td>
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<tr>
<td>All</td>
<td>6 (8.5)</td>
<td>6 (5.9)</td>
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<tr>
<td>Absidia species</td>
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<td>Other</td>
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<td>All</td>
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<tr>
<td>Fusarium species</td>
<td>2 (33.3)</td>
<td>2 (25.0)</td>
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</table>

**NOTE.** IFIs were not mutually exclusive; patients could have >1 IFI. Two hundred nineteen patients had only 1 IFI. Fourteen patients had 2 concomitant IFIs: 3 had IFIs due to 2 different Candida species, 4 had IFIs due to Candida and Aspergillus species, 4 had IFIs due to 2 different Aspergillus species, and 3 had IFIs due to Rhizopus species plus C. glabrata, A. fumigatus, or an unknown Aspergillus species. One HSCT recipient had 3 concomitant IFIs due to 2 different Candida species and an unknown yeast.

* Included 59 recipients of HSCTs from HLA-matched, unrelated donors; 8 recipients of HSCTs from haploidentical donors; and 31 recipients of HSCTs from HLA-mismatched donors.
* One case of IFI due to Candida guilliermondii was observed.
* Endemic fungi included 1 case involving Histoplasma species.
* Other yeasts included Saccharomyces species (2 cases) and Malassezia and Trichosporon species (1 case each).

Outcomes. A total of 35 of 234 HSCT recipients with IFI were lost to follow-up during the 12-week observation period. Of the remaining 199 patients, 93 (46.7%) died. Survival did not differ when patients were analyzed on the basis of HSCT type (allogeneic transplant from a matched, related donor vs. allogeneic transplant from other donor vs. autologous transplant; P = .85). For patients with only 1 IFI, after exclusion of patients who were lost to follow-up, IFI due to other molds was associated with the highest 12-week mortality rate (80.0% [12 of 15 patients]), followed by zygomycosis (64.3% [9 of 14 patients]), plus caspofungin was the most frequently used type of this particular combination regimen (47 patients [69.1%]).
patients) and IC (48.9% [22 of 45 patients]). Patients with IA had the lowest 12-week mortality rate in this study (35.5% [38 of 107 patients]). The 6-week survival rate was significantly better for HSCT recipients with IA, followed by those with IC and those with IFI due to Zygomycetes or other molds, who had the highest mortality rate (P < .001) (figure 4A). Response to treatment was assessed by investigators at 12 weeks after the diagnosis of IFI (figure 4B). The majority of HSCT recipients with IC (42 [67.7%] of 62 patients) and with IA (94 [63.5%] of 148 patients) were reported to have responded (completely or partially) to the administered therapy. In contrast, 10 (55.6%) of 18 patients with zygomycosis and 6 (35.3%) of 17 with IFI due to other molds demonstrated a worsening of their clinical status at follow-up.

In 6-week survival analyses performed for HSCT recipients with IA only, there were no significant differences observed in the survival rate based on the certainty of diagnosis (proven vs. probable), the HSCT type (allogeneic vs. autologous), or the interval between HSCT and diagnosis (≤40 days vs. >40 days; data not shown). However, there appeared to be a trend toward worse outcome at 6 weeks among allogeneic HSCT recipients with IA who received myeloablative conditioning (P = .07).

We performed bivariate analyses to assess risk factors for death at 6 weeks after the diagnosis of IA in allogeneic HSCT recipients; the variables examined are detailed in Methods. Nonmyeloablative conditioning (P = .01) and absence of mechanical ventilation or/and hemodialysis (P = .01) were associated with improved survival rates. Because the variables examined were associated with the interval between HSCT and diagnosis, we performed separate analyses based on the timing of the diagnosis of IA. For the early time period (i.e., ≤40 days after transplantation), data on 30 patients with IA were included in bivariate and multivariate analyses. The bivariate 6-week exploratory analyses revealed trends toward improved survival associated with a lack of severe organ failure (as evidenced by dialysis and mechanical ventilation; P = .08) and receipt of a nonmyeloablative conditioning regimen (P = .07). When these variables were introduced in a multivariate model, only severe organ dysfunction (OR, 1.60; P = .01) continued to demonstrate a trend toward higher mortality risk. Similarly, in bivariate analyses for late diagnoses (i.e., >40 days after transplantation), survival rates seemed to be better for patients who had received a nonmyeloablative condition regimen (P = .12) and who did not require dialysis or/and mechanical ventilation (P = .02).

DISCUSSION

We performed this multicenter, prospective, observational study to evaluate the contemporary epidemiologic characteristics, clinical presentations, and outcomes of IFI in 234 adult HSCT recipients during the period 2004–2007. Important findings include persistently high rates of IA, with possible improvements in IA-associated mortality, and poor outcomes associated with other fungal infection after HSCT.

Mortality rates for HSCT recipients with IA have historically been as high as 80%, although most studies were performed before the extensive use of voriconazole for the treatment of IA [3, 9, 10]. However, recent data suggest that outcomes appear to be improving [11]. We report 6- and 12-week mortality rates of 21.5% and 35.5%, respectively, among HSCT recipients with IA, which is markedly improved over rates from prior reports of outcomes during the 1990s. The observed 12-week survival rate is consistent with that reported by Herbrecht et al. [12] in the original validation trial of voriconazole for the treatment of IA [3, 9, 10]. However, recent data suggest that outcomes appear to be improving [11]. We report 6- and 12-week mortality rates of 21.5% and 35.5%, respectively, among HSCT recipients with IA, which is markedly improved over rates from prior reports of outcomes during the 1990s. The observed 12-week survival rate is consistent with that reported by Herbrecht et al. [12] in the original validation trial of voriconazole for the treatment of IA, although only a minority of patients in that study had undergone HSCT. An analysis of that study suggested that assessment of clinical outcome and mortality at 6 weeks after diagnosis may be more reflective of IA-associated mortality [13]; the 21.5% estimated mortality rate in our data set
approximates the rates in prior studies reporting relatively recent outcomes and is likely to be a better estimate of attributable mortality. Improved contemporary outcomes likely reflect improved diagnostic and therapeutic modalities, compared with older patient series. In addition, it is likely that the potent and well-tolerated antifungal agents that are newly available have improved outcomes.

A number of host variables have been associated with both improved survival rates (e.g., nonmyeloablative conditioning regimens and use of peripheral blood as a stem cell source) and higher mortality (e.g., receipt of transplants from HLA-mismatched donors, neutropenia, abnormal renal function, elevated bilirubin level, and use of corticosteroids) in allogeneic HSCT recipients with IA [11, 14]. In our study, receipt of a nonmyeloablative conditioning regimen and absence of severe organ failure appeared to be protective in bivariate analyses of 6-week mortality risk factors for allogeneic HSCT recipients with IA. Of note, only the absence of severe organ dysfunction 40 days after transplantation was significantly associated with improved outcome (P = .02), perhaps because of the small number of patients included in these analyses.

More than one-half of the patients we describe were enrolled by only 2 institutions; this may have skewed the presented outcomes and created further biases. For instance, almost one-half of the allogeneic HSCT recipients described in this study came from a single institution. When secondary survival analyses were performed that excluded the 93 patients who presented to that center, survival outcomes were similar to those observed in the overall patient population (data not shown). The majority of autologous HSCT recipients with an IFI (50 [68.5%] of 73 patients) were reported by a single center. Autologous HSCT recipients in this study had received a diagnosis of multiple myeloma (68.5%), had experienced a relapse of their underlying disease (60.3%), had a history of prior HSCT (56.2%), and had received corticosteroids (75.3%). This, in part, may have had an impact on the high number of cases of IA and the associated high mortality rate observed among autologous HSCT recipients in our study [15, 16]. Although differences in patient risks may, in part, explain this finding, there are obviously differences in clinical approaches and diagnostic aggressiveness between transplantation centers; these factors should be addressed in the design and conduct of future registries and clinical trials.

Although the frequency of IA remained relatively stable during 2005–2006, there seemed to be a trend toward higher numbers of IFIs due to Zygomycetes and other molds. This trend, first described in patients who received transplants after 1995, probably reflects the higher-risk transplantations performed (leading to a more immunosuppressed patient population) and the extensive use of prophylactic treatment with agents that have activity against Aspergillus species (e.g., voriconazole) [4, 9]. Availability of voriconazole as a therapeutic agent may also lead to diagnostic “bias,” with innately resistant infections (zygomycosis) being diagnosed today; these infections may have been treated empirically with amphotericin B products in the 1990s. Of note, conventional amphotericin B was minimally used in this study. Because this reflects the practice observed in 16 different medical centers, it appears that conventional amphotericin B has largely been replaced by the lipid formulations of amphotericin B and the new third-generation azoles.

A shift toward late diagnosis of IA (i.e., >40 days after HSCT) among allogeneic HSCT recipients has been reported by multiple centers [3, 17, 18]. Almost two-thirds of IA cases among allogeneic HSCT recipients in this study were observed >40 days after transplantation. However, a number of IA cases among recipients of allogeneic (37.1%) and autologous (48.9%) HSCTs were observed ≤40 days after transplantation. This suggests that IA remains a significant problem soon after trans-
plantation, despite the routine administration of prophylactic therapy and the aggressive monitoring of these patients. In accordance with already published data [9], we found that IFI due to Zygomyces or other molds remains a later complication for both allogeneic and autologous H SCT recipients.

Although the majority of patients with IC responded to the administered treatment, IC was associated with a 12-week mortality rate of 48.9%. We believe that this most likely reflects the underlying compromised immune status and organ function of patients who develop Candida infection; the true attributable mortality rate is unclear in this registry. Because of the small number of patients with IC in our study, we were not able to obtain data on potential risk factors associated with mortality in HSCT recipients with IC. IFIs due to Zygomyces or other molds were associated with the highest mortality rates in our study (64.3% and 80.0%, respectively). This may be the result of the cumbersome, occasionally late diagnosis and suboptimal therapeutic modalities available for the management of these infections. Clearly, more studies need to be performed that address the diagnostic approaches to and treatment of IFI due to molds other than Aspergillus species.

This study has a number of limitations. Because of the design of this registry, the total number of transplants performed at each center is not recorded; thus, the incidences of the different IFIs cannot be calculated. Although this is a prospective data collection registry, the database is observational in nature and subject to a number of potential biases. Although data on antifungal therapy administered ≥30 days before diagnosis of the IFI were collected, it is not possible to clearly distinguish between prophylactic, preemptive, and empirical therapy. Information on supportive care of HSCT recipients at different centers was not available. In addition, information on the cytomegalovirus serostatus of donors and recipients was not reported. Finally, the results are limited to patients enrolled from selected centers in North America, and as such, they may not reflect practices from other parts of North America or around the globe.

Overall, we report that IA remains the most commonly identified IFI among HSCT recipients, although survival at 12 weeks has significantly improved. IFIs due to Candida species, Zygomyces, and other molds were also observed and were associated with high mortality rates. As practices in the HSCT setting change, and as new diagnostic and therapeutic modalities are added to the armamentarium of clinicians, this field will continue to set challenges and require answers through future prospective, multiple-center studies.

**Figure 4.** A, Twelve-week survival outcome for invasive fungal infection (IFI) in patients with 1 IFI; *P* value is calculated by log-rank test. B, Investigator-judged response to therapy for IFI in hematopoietic stem cell transplant recipients 12 weeks after transplantation. IA, invasive aspergillosis; IC, invasive candidiasis.
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