Prospective Surveillance for Invasive Fungal Infections in Hematopoietic Stem Cell Transplant Recipients, 2001–2006: Overview of the Transplant-Associated Infection Surveillance Network (TRANSNET) Database

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(See the article by Pappas et al, on pages 1101–1111.)

Background. The incidence and epidemiology of invasive fungal infections (IFIs), a leading cause of death among hematopoeitic stem cell transplant (HSCT) recipients, are derived mainly from single-institution retrospective studies.

Methods. The Transplant Associated Infections Surveillance Network, a network of 23 US transplant centers, prospectively enrolled HSCT recipients with proven and probable IFIs occurring between March 2001 and March 2006. We collected denominator data on all HSCTs preformed at each site and clinical, diagnostic, and outcome information for each IFI case. To estimate trends in IFI, we calculated the 12-month cumulative incidence among 9 sequential subcohorts.

Results. We identified 983 IFIs among 875 HSCT recipients. The median age of the patients was 49 years; 60% were male. Invasive aspergillosis (43%), invasive candidiasis (28%), and zygomycosis (8%) were the most common IFIs. Fifty-nine percent and 61% of IFIs were recognized within 60 days of neutropenia and graft-versus-host disease, respectively. Median onset of candidiasis and aspergillosis after HSCT was 61 days and 99 days, respectively. Within a cohort of 16,200 HSCT recipients who received their first transplants between March 2001 and September 2005 and were followed up through March 2006, we identified 718 IFIs in 639 persons. Twelve-month cumulative incidences, based on the first IFI, were 7.7 cases per 100 transplants for matched unrelated allogeneic, 8.1 cases per 100 transplants for mismatched-related allogeneic, 5.8 cases per 100 transplants for matched-related allogeneic, and 1.2 cases per 100 transplants for autologous HSCT.

Conclusions. In this national prospective surveillance study of IFIs in HSCT recipients, the cumulative incidence was highest for aspergillosis, followed by candidiasis. Understanding the epidemiologic trends and burden of IFIs may lead to improved management strategies and study design.

Invasive fungal infections (IFI), especially invasive aspergillosis (IA), have emerged as a leading cause of morbidity and infection-related mortality among hematopoeitic stem cell transplant (HSCT) recipients [1]. Estimates of the incidence and prevalence of these infections have varied substantially, because longitudinal surveillance for IFI has not been conducted in that

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Table 1. Characteristics of Hematopoietic Stem Cell Transplant (HSCT) Recipients Who Developed ≥1 Invasive Fungal Infection (IFI) and a Description of All IFI Cases

| Variable	Surveillance cohort	Incidence cohort
HSCT recipients		
No. of HSCT recipients	875	639
Age, median years (range)	49 (0.3–79)	50 (0.3–76)
Pediatrics patients (age <18 years)	69 (8)	54 (9)
Male sex	520 (60)	376 (59)
Race		
White	705 (87)	507 (87)
Black	58 (7)	41 (7)
3-Month mortality	445 (51)	325 (51)
Type of first transplant		
Autologous	184 (21)	134 (21)
Syngeneic	1 (0.1)	0 (0)
Allogeneic Matched Related	336 (38)	232 (36)
Allogeneic Mismatched Related	55 (6)	47 (7)
Allogeneic Unrelated	298 (34)	226 (35)
Stem cell source:		
Marrow	168 (19)	114 (18)
Cord blood	22 (3)	19 (3)
Peripheral blood	684 (78)	506 (79)
Pretransplantation conditioning		
Myeloablative	606 (70)	431 (68)
Nonmyeloablative	261 (30)	202 (32)
Unknown	3 (0.3)	6 (1)
IFI cases		
No. of cases	983	718
Neutropenia[a] within 60 days before onset	563 (57)	442 (62)
Graft-versus-host disease within 60 days before onset	590 (61)	427 (60)
Grade I–II	199 (34)	133 (31)
Grade III–IV	292 (50)	229 (54)
Unspecified	99 (17)	65 (15)
Invasive aspergillosis	425 (43)	301 (42)
Aspergillus fumigatus	187 (44)	134 (45)
Aspergillus terreus	22 (5)	17 (6)
Aspergillus niger	36 (9)	26 (9)
Aspergillus flavus	31 (7)	25 (8)
Multiple *Aspergillus* species	27 (6)	17 (6)
Other *Aspergillus* species	13 (3)	12 (4)
Unspecified *Aspergillus* species	109 (26)	70 (23)
Invasive candidiasis	276 (28)	217 (30)
Candida albicans	55 (20)	42 (19)
Candida glabrata	92 (33)	70 (32)
Candida krusei	17 (6)	14 (7)
Candida parapsilosis	39 (14)	35 (16)
Candida tropicalis	23 (8)	16 (7)
Candida lusitaniae	4 (2)	4 (2)
Multiple *Candida* species	15 (5)	11 (5)
Other *Candida* species	1 (0.4)	1 (0.5)
Unspecified *Candida* species	30 (11)	24 (11)
Zygomycosis	77 (8)	66 (9)
Other molds[b]	66 (7)	36 (5)
Unspecified molds	55 (6)	40 (6)
Fusariosis	31 (3)	22 (3)
Pneumocystosis	21 (2)	13 (2)
Other non-*Candida* yeast[c]	16 (2)	13 (2)
Endemic fungi[d]	6 (0.6)	3 (0.4)
Cryptococcosis	6 (0.6)	3 (0.4)
Unspecified yeasts	4 (0.4)	4 (0.6)

NOTE. Data are no. (%) of patients or cases, unless otherwise indicated.

[a] Neutropenia was defined as ≤500 polymorphonuclear cells/dL.

[b] Other molds included *Acremonium, Alternaria, Arthrographis, Bipolaris, Chaetomium, Chrysosporium, Cladophialophora, Curvularia, Exophiala, Exserohilum, Microsascus, Paecilomyces, Penicillium, Phialemonium, Pseudallescheria, Scedosporium, Scopulariopsis,* and *Trichoderma* species.

[c] Other non-*Candida* yeast included *Geotrichum, Malassezia, Rhodotorula, Saccharomyces, Trichosporon,* and *Zygoascus.*

[d] Endemic fungi included *Histoplasma, Blastomyces,* and *Coccidioides.*
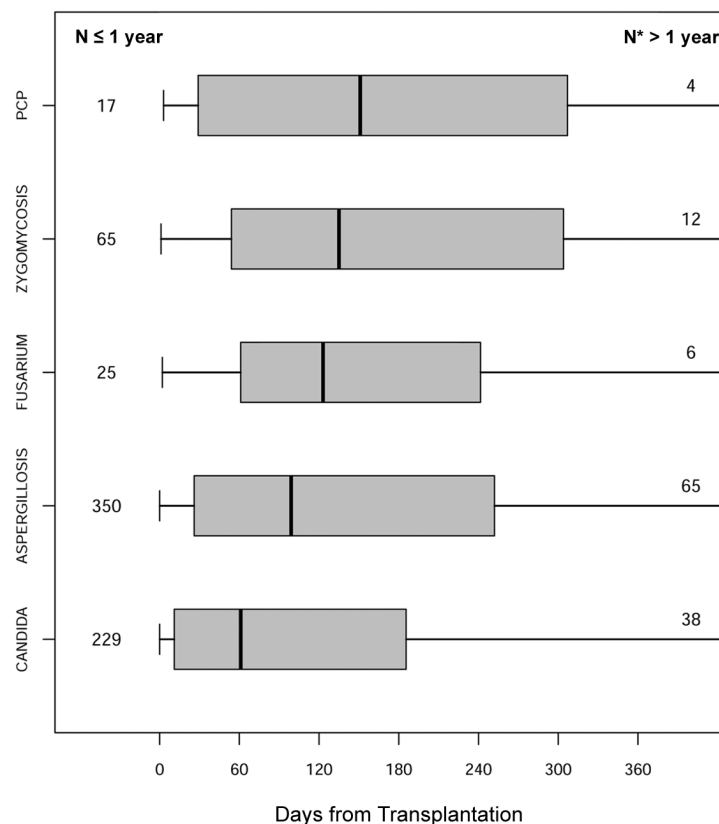
Figure 1. Distribution of time to invasive fungal infection (IFI) stratified by infection type (all IFI cases in surveillance cohort). N, number of IFIs in first year; N*, number of IFIs occurring after 1 year; PCP, pneumocystosis.

patient population [2]. Consensus definitions for the diagnosis of IFIs, which are based on the synthesis of host, microbiologic, and clinical factors, have allowed investigators to compare case descriptions across different studies and institutions [3]. However, most estimates of the incidence and epidemiology of IFIs in HSCT recipients have been derived from studies done in single institutions or from retrospective surveys that have focused on specific fungi or specific types of HSCTs [4–18]. Thus, institution-specific issues, such as transplant patient populations, practices, or even environmental exposures, preclude generalization of incidence across multiple centers, geographical regions, or countries. Furthermore, retrospective assessment of the incidence of IFIs with use of discharge databases or death records relies on insufficient data that could lead to inaccurate estimates, especially with respect to invasive mold infections [19, 20].

To that end, the Transplant Associated Infections Surveillance Network (TRANSNET), a consortium of 23 US academic transplant centers (22 contributing HSCTs) and the Centers for Disease Control and Prevention (CDC), was launched in 2001 to determine the burden of IFI among transplant recipients [20]. Here, we report an overview of the incidence of these infections among HSCT recipients by aggregating 5-year data,

collected prospectively from all the sites of this network. These data provide useful estimates of the current incidence and burden of fungal infections in the HSCT population and may form the basis for improving direct efforts in prevention, risk stratification, and management.

METHODS

TRANSNET is a sentinel surveillance system collaboratively administered by the CDC and the coordinating center at the University of Alabama at Birmingham. The network comprises 23 transplant centers throughout the United States that perform HSCTs and/or organ transplantation. Prospective surveillance was conducted from March 2001 through March 2006. Cases of IFI that occurred among organ transplant and HSCT recipients were identified to describe the epidemiology of these infections. All sites received local institutional review board approval prior to the enrollment of patients. This report includes data from the 22 transplant centers that contributed data regarding HSCT recipients.

Case definition and ascertainment. All identified proven or probable cases were captured during the surveillance period, regardless of the date of transplantation. Cases were defined

Table 2. Characteristics of Hematopoietic Stem Cell Transplant (HSCT) Recipients in the Incidence Cohort, 2001–2005

Characteristic	HSCT recipients (n = 16,200)
Age, median years (range) (n = 15,390)	50 (0.1–85)
Pediatric patients (age <18 years)	1386 (9)
Male sex (n = 15,877)	9287 (59)
Race (n = 15,623)	
White	12855 (82)
Black	1185 (8)
Deaths within 12-months after transplantation (n = 15,820)	3576 (22)
Donor type:	
Autologous	9534 (59)
Syngeneic	38 (0.2)
Allogeneic matched related	3628 (22)
Allogeneic mismatched related	474 (3)
Allogeneic unrelated	2526 (16)
Stem cell source:	
Marrow	2382 (15)
Cord blood	171 (1.0)
Peripheral blood	10078 (62)
Peripheral and marrow	58 (0.4)
Cord and marrow	2 (0.01)
Unknown	3509 (22)
Pretransplantation conditioning	
Myeloablative	9199 (57)
Nonmyeloablative	3386 (21)
Unknown	3615 (22)

according to the consensus definitions developed by the Invasive Fungal Infections Cooperative Group of the European Organization for Research and Treatment of Cancer (EORTC) and the Mycoses Study Group (MSG) [3]. Patients who met the definition of possible infection and those with a preexisting IFI that relapsed after transplantation were not included.

To detect cases, investigators received information from attending physicians, participated in clinical rounds, and reviewed clinical microbiology, serology, medical, and pathology records on a weekly basis. For purposes of this study, we did not distinguish among sites that used routine serologic screening (eg, weekly serum *Aspergillus* galactomannan testing). At each site, data were entered into a standardized form that was forwarded to the coordinating center. A data review committee reviewed each case to determine its validity and inclusion into the dataset.

Investigators collected the following data on all HSCT recipients who developed an IFI, regardless of the date of transplantation (surveillance cohort): date of infection onset, site(s) of infection, clinical signs, method(s) of diagnosis, coinfections, comorbid conditions, immunosuppressive medications received, antifungals administered, and outcome. The date of diagnosis was defined as the date on which the first diagnostic

culture or examination related to the IFI was performed. For cases in which the diagnosis was established during postmortem examination, the date of death was considered to be the day of diagnosis. Neutropenia was defined as an absolute polymorphonuclear count of <500 cells/mm^3. Investigators followed established definitions for defining graft-versus-host disease (GvHD) [21].

Investigators collected additional information on all HSCT recipients who underwent transplantation from March 2001 through September 2005 (incidence cohort) and included demographic data (age, sex, and race/ethnicity), date and type of transplant (autologous, syngeneic, or allogeneic), relatedness and type of HLA-matching (matched-related [MRD], mismatched-related [MMR], or unrelated [URD] donor), and pretransplantation conditioning regimen (myeloablative vs nonmyeloablative). Study start and stop times differed across sites for the HSCT cohort; 21 of the 22 sites contributed consistently from May 2002 through April 2005. Follow-up information for the incidence cohort included date of last follow-up and patient status, which were used to calculate the cumulative incidence (CI) curves.

An internal audit was performed to enhance the case-finding ability of each site. At the conclusion of prospective surveil-
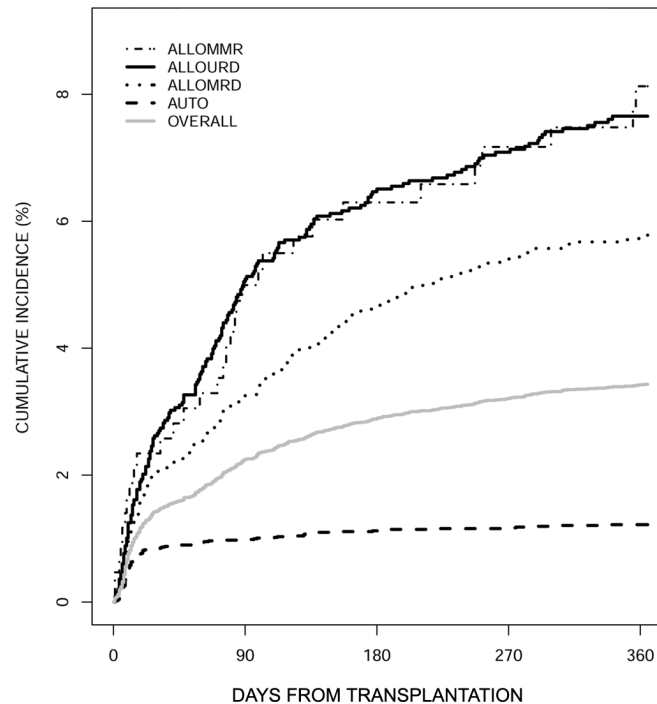
Figure 2. Cumulative incidence curves for any invasive fungal infection among hematopoietic stem cell transplant (HSCT) recipients in the Transplant Associated Infections Surveillance Network surveillance cohort, stratified by type of HSCT. ALLOMMR, allogeneic mismatched-related donor; ALLOMRD, allogeneic matched-related donor; ALLOURD, allogeneic unrelated donor; AUTO, autologous.

lance, each site was asked to review the records of randomly selected patients from their site who underwent HSCT during the surveillance period but were not identified as having an IFI. We selected 20%–30% of the HSCT recipients who received a transplant from an HLA-related or unrelated donor to generate this list, because these groups had high observed incidence rates. The site investigator reviewed each patient record to confirm the infection status of the selected patient. If a previously unidentified case of IFI was discovered, the case was registered with the central unit and a case report form was completed. Following this methodology, few additional cases (<5% of total cases) were identified.

Microbiological methods. Available cultures and histopathological specimens were processed at the participating hospitals. Species identification was performed using routine methods at the local laboratories. Fungal isolates were forwarded to the UAB Fungal Reference Laboratory and the CDC Mycotic Diseases Branch, where the species identification was confirmed. Patients with invasive aspergillosis whose cultures yielded an *Aspergillus* species that was not further identified or whose diagnosis was based on positive galactomannan assay results as the only microbiologic criteria were classified as having infection due to unspecified *Aspergillus* species. Culture-negative cases in which histopathologic findings showed acute branching hyphae consistent with an invasive mold were classified as being due to unspecified molds.

Data analysis. Descriptive analyses were performed for all IFI cases occurring among HSCT recipients detected during the surveillance period. Box-and-whisker plots were generated to summarize time to IFI from transplant.

The CI of IFI occurring among the incidence cohort was calculated on the basis of time to first IFI. These calculations accounted for the competing risks of infection-free death, re-transplantation, and relapse of underlying disease. The 12-month CIs for first IFI of any type for all transplants, as well as 12-month CIs for first IFI within each specific transplant type were also calculated. IFI-specific and site-specific CIs were calculated by pooling all transplant types. CIs were estimated using the cmprisk risk package, version 2–1-7 , in R , version 2.6.1. IFI-specific 1-year survival estimates were calculated using the Kaplan-Meier method.

The trend of CIs during the surveillance period was also described. We divided the incidence cohort into 9 separate and sequential subcohorts, based on the 4-month time period during which an individual's transplantation occurred. One site was omitted because it did not report transplant data in 2004 and 2005. The 12-month CIs for first IFI for each subcohort were calculated and then plotted against the time periods. We also stratified sites into 2 groups that were based on the proportion of all transplants that used an allogeneic donor. The 11 sites with the highest proportions of allogeneic transplants (44%–91%) were compared with the 10 sites with the lowest
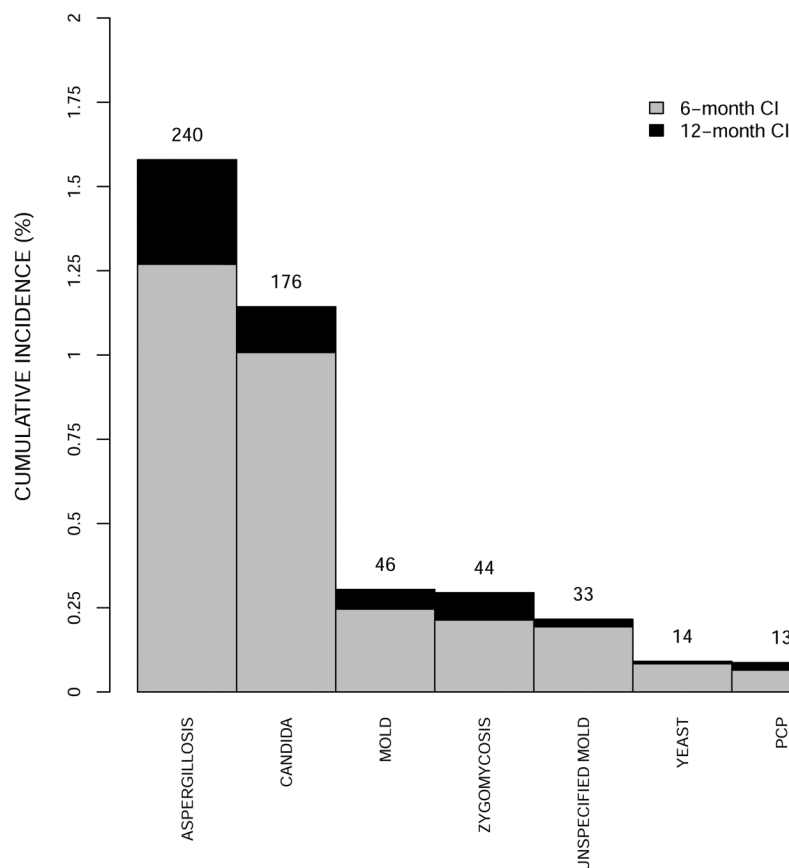
Figure 3. Six-month and 12-month cumulative incidence (CI) for each invasive fungal infection (IFI) type in the incidence cohort. The number of IFIs contributing to the 12-month CI is given for each column. ASPERG, aspergillosis; MOLD, other molds *(Acremonium, Alternaria, Arthrographis, Bipolaris, Chaetomium, Chrysosporium, Cladophialophora, Curvularia, Exophiala, Exserohilum, Microsascus, Paecilomyces, Penicillium, Phialemonium, Pseudallescheria, Scedosporium, Scopulariopsis,* and *Trichoderma* species); PCP: pneumocystosis; UNSPEC MOLD, unspecified molds; YEAST, other non-*Candida* yeast *(Geotrichum, Malassezia, Rhodotorula, Saccharomyces, Trichosporon,* and *Zygoascus* species); ZYGO, zygomycosis.

proportions (2%–39%). The CI trend among the 9 subcohorts for *Aspergillus* and *Candida* IFIs among all sites was also described.

RESULTS

Invasive fungal infections among stem cell transplant recipients. During the study period, we detected 983 proven and probable IFI cases among 875 HSCT recipients (Table 1). The median age of case-patients was 49 years, and 60% were male; 184 (21%) had received autologous transplants, and 689 (78%) had received allogeneic transplants. Of the latter group, 336 case-patients (38%) had an MRD, 55 (6%) had an MMRD, and 298 (34%) had a URD. Myeloablative pretransplant conditioning was performed for 606 (70%). In the 60 days prior to receipt of an IFI diagnosis, 563 case-patients (57%) were neutropenic (<500 cells/mm³), and 590 (61%) had GvHD (any grade).

Five hundred and fifty-four (56%) of the cases were proven and 429 (44%) were probable. Invasive aspergillosis was the

most common IFI (425 cases; 43%), followed by invasive candidiasis (276 cases; 28%) and zygomycosis (77 cases; 8%) (Table 1). *Aspergillus fumigatus* caused 187 (44%) of the 425 cases of aspergillosis, 27 (6%) of the cases were caused by >1 *Aspergillus* species, and 109 (26%) were caused by unidentified species. Of note, 55 (6%) of the cases were due to unspecified molds. Among 276 patients with invasive candidiasis, *Candida glabrata* was the most common organism (92 cases; 33%), followed by *Candida albicans* (55 cases; 20%).

Timing of infection. Median time after transplantation to onset of IFI was 61, 99, 123, and 135 days for candidiasis, aspergillosis, fusariosis, and zygomycosis cases, respectively (Figure 1). Of the 80 *Aspergillus* infections in autologous HSCT recipients, 40 (50%) and 53 (66%) occurred within 1 and 4 months after receipt of transplant, respectively. Of 70 invasive *Candida* infections in autologous HSCT recipients, 46 (66%) and 52 (74%) occurred in within 1 and 4 months after receipt of transplant, respectively. Among allogeneic HSCT recipients, 72 (22%) and 178 (53%) of 335 aspergillosis cases occurred 1 and 4 months
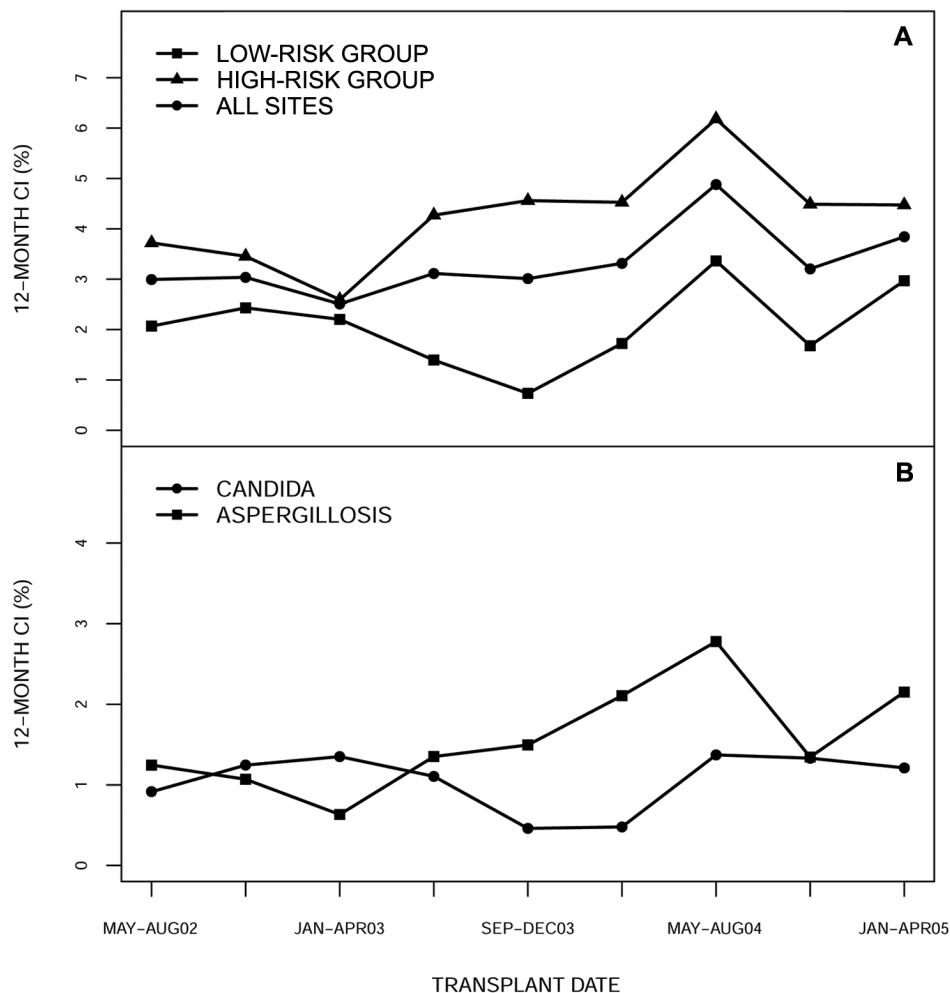
Figure 4. Trend in 12-month cumulative incidence (CI) *(A)* for first invasive fungal infection (IFI) among each of 9 subcohorts, as determined by transplantation date, and stratified by inclusion of the transplant center into high-risk (≥40% allogeneic hematopoietic stem cell transplant [HSCT] recipients) or low-risk (<40% HSCT recipients) groups and (B) for *Candida* and *Aspergillus* infections.

after receipt of transplant, respectively. Seventy-five (45%) of 167 aspergillosis cases in MRD HSCT recipients and 86 (61%) of 140 aspergillosis cases in URD HSCT recipients, occurred within 4 months of receipt of transplant. Fifty-seven percent of aspergillosis cases that occurred in individuals who received myeloablative pretransplantation conditioning occurred within 4 months of transplant receipt, compared with 52% of cases in individuals with nonmyeloablative conditioning.

Incidence cohort. From March 2001 through September 2005, 16,220 patients underwent at least 1 HSCT procedure at 1 of the surveillance sites (Table 2). Follow-up information was available for 15,820 (98%) of the patients, representing 11,563 persons-years of follow up. Among autologous HSCT recipients in the cohort, all-cause mortality was 5% and 13% at 4 and 12 months after receipt of transplant, respectively. Among allogeneic HSCT recipients, all-cause mortality was 19% and 36% at 4 and 12 months after receipt of transplant, respectively. IFIs

occurred in 639 patients in the incidence cohort, and a description of 718 IFIs that occurred in this cohort is included (Table 1).

Twelve-month cumulative incidence. The 12-month CI was calculated for 15,820 incidence cohort patients for whom follow-up data were available. During the 12 months after receipt of transplant, 1988 patients (12.6%) experienced relapse of their underlying disease, 120 underwent retransplantation, 2336 died, and 524 developed an IFI prior to having any of these competing risks (ie, relapse, retransplantation, or death).

The overall 12-month CI for any IFI was 3.4% (range by site, 0.9%–13.2%). IFI incidence was lowest among autologous HSCT recipients, with a 12-month CI of 1.2%. Among allogeneic transplant recipients, the 12-month CIs for MRD, URD, and MMR donors were 5.8%, 7.7%, and 8.1%, respectively (Figure 2).

Although 21 sites contributed MMR transplants to the HSCT

cohort, only 6 contributed >20 MMR transplants each; these 6 sites contributed nearly 80% of all reported MMR transplants. The 12-month CIs for these 6 sites ranged from 3.1% through 20.6%. Twenty-one sites contributed URD transplants, with 17 sites contributing at least 20 URDs (12-month CI range, 0%–14.3%). All 22 sites contributed at least 1 MRD transplant, with 21 sites contributing at least 20 (12-month CI range, 0%–16.6%). All sites contributed at least 20 autologous transplants (12-month CI range, 0%–6.9%).

The 6-month and 12-month CIs for aspergillosis were 1.3% and 1.6%, respectively (Figure 3), compared with 1.0% and 1.1%, respectively, for candidiasis. The incidence of non-*Aspergillus* mold infections was very low (12-month CI, ≤0.3%).

Figure 4A shows the trend of 12-month CI among each of the 9 sequential subcohorts for 21 sites (the 11 sites that performed the highest proportion of allogeneic transplantations and the 10 sites that performed the lowest proportion). For most time periods, the CIs ranged from 2.5% through 3.3%. However, the subcohort of patients who underwent transplantation from May through August 2004 had a higher CI (4.9%). This increase was most pronounced for the 11 sites that performed transplantations for the patients at highest risk; 6.0% for the May–August 2004 subcohort. The CIs for all sites decreased in subsequent cohorts to 3.2% and 3.8%.

The trend of IFI-specific 12-month CI for each of these 9 subcohorts is shown in Figure 4B. The CI for *Candida* infections was stable throughout the study period. In contrast, the CI for invasive aspergillosis increased steadily from 0.6% in the subcohort that received transplants during the period January–April 2003, to 2.8% in the subcohort that received transplants during the period May–August 2004. The aspergillosis CI was lower in the last 2 subcohorts.

Mortality. Overall 1-year survival among the HSCT cohort was the lowest for patients with *Fusarium* infections (6.3%) and for patients with aspergillosis (25.4%); patients with zygomycosis (28.0%) and candidiasis (33.6%) had slightly higher survival rates.

DISCUSSION

The burden of IFIs in the HSCT population has been difficult to estimate. Our current understanding of the epidemiology and incidence of these infections is largely based on data collected in the 1980s and 1990s [4–17] and data collected from single institutions that used imprecise methods to identify cases. However, these data were heavily influenced by local patterns of care and may not represent a true picture of IFI in US transplant centers. By contrast, these data are multicenter, geographically diverse, represent all major stem cell transplant types, and describe prospective surveillance for ~20% of the

80,000 persons who underwent stem cell transplantation in the United States during the study period [22].

The overall IFI incidence was low (3.4%), although there was considerable variability across institutions (range by site, 0.9%–13.2%). Other single-center and retrospective studies have reported higher incidences [4–17]. We believe that the lower incidence reported here more closely approximates the true burden of proven and probable IFI among HSCT recipients in the United States. Compared with smaller studies, these data report rates from tertiary care centers performing transplantations for high-risk patients and from institutions performing transplantations for a broad spectrum of patients. The site-specific variation in incidence may reflect varying methods in detection and diagnosis, differences in the patient population, or differences in transplantation practices at individual sites.

This is also the first study to calculate CIs to evaluate whether the incidence of IFI changed over time. This method, which accounts for competing risks of IFI among separate subcohorts, is a more appropriate way of measuring transplant-associated risk. We found that the subcohort that received transplants during the period May–August 2004 had the highest CI (4.9%). This increase was largest at the sites that performed the most allogeneic stem cell transplantations, but the CI also increased at sites that performed fewer high-risk transplantations. The CI of aspergillosis increased, whereas that of invasive candidiasis remained stable. Reasons for the observed increase for aspergillosis at high-risk sites are unclear but may reflect shifts in the type of transplantations performed at these centers, subtle shifts in the immunosuppression practices in management of these patients, or changes in diagnostic accuracy for invasive mold infections. Importantly, the incidence of IFIs did not decrease, despite the common practice of antifungal prophylaxis; on the contrary, IFIs may have increased among some subgroups.

We found that invasive molds, particularly *Aspergillus* species, were the dominant fungi causing infection and were associated with a high crude mortality within 90 days after diagnosis. It is notable that aspergillosis was seen late in many patients in our cohort, which is consistent with observations from previous studies [4, 16]. These findings underscore the difficulty in preventing these infections, especially in the outpatient setting, where exposures to mold in the environment are likely to be frequent.

Our study also demonstrated that non-*Aspergillus* mold infections remained relatively uncommon. However, a large number of IFI cases (109 attributed to *Aspergillus* species and 55 attributed to other pathogens) were due to molds that were not firmly identified, probably because culture-based diagnostic methods were not used (Table 1). These results are similar to those of recent single-center studies that used autopsies to iden-

tify IFIs in patients with hematologic malignancies [23, 24]. Thus, the precise epidemiology of invasive mold infections will remain uncertain until validated, sensitive and specific non–culture-based diagnostic methods become available.

Finally, candidiasis, which was relatively common among this patient population during the 1980s and early 1990s, represented a minority (28%) of IFIs in this group. Non-*albicans Candida* species accounted for almost 70% of these infections. Widespread use of azole prophylaxis has likely influenced the decreased incidence and shift in epidemiology in the HSCT setting [25, 26], although other factors may play a role.

These data are limited for several reasons. First, although investigators at participating sites were encouraged to use standardized methods to identify cases, there was variability between sites regarding the intensity of diagnostic measures pursued that may partially account for the wide range of incidence between sites. Second, we probably underestimated the true burden of IFIs overall, because possible cases (according to EORTC/MSG criteria) were not included, and the current culture and histopathological methods are not very sensitive. Autopsy rates in this patient population have decreased dramatically [23], making this issue especially salient. Finally, information regarding double and tandem HSCTs (eg, sequential allogeneic and autologous) was not routinely obtained.

It is important to emphasize that this study was designed primarily to establish estimates of disease burden in the United States. The study was not designed to critically assess important risk factors for the development of IFI, nor to assess rates of infection or clinical outcome on the basis of antifungal prophylaxis and therapy, respectively. Moreover, the critical risk assessment data that were gathered from the denominator (all patients who received transplants) were incomplete and therefore of limited use. Similarly, detailed antifungal prophylaxis and treatment data were not available for all patients who developed an IFI. These analyses, together with a description characterizing the fungal isolates from these patients, are the subject of separate analyses.

Although the epidemiology of IFIs in highly immunosuppressed HSCT recipients is constantly evolving, in part because of changes in antifungal prescribing patterns, these data demonstrate that IFIs in HSCT recipients are still associated with high crude mortality. The data provide a important reference for the current epidemiology and incidence of IFIs. Continued surveillance for IFIs is warranted in this patient population, and better diagnostic and treatment modalities are needed.

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