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Incidence of invasive aspergillosis following hematopoietic stem cell and solid organ transplantation: interim results of a prospective multicenter surveillance program

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The incidence of invasive aspergillosis was estimated among 4621 hematopoietic stem cell transplants (HSCT) and 4110 solid organ transplants (SOT) at 19 sites dispersed throughout the United States, during a 22 month period from 1 March 2001 through 31 December 2002. Cases were identified using the consensus definitions for proven and probable infection developed by the Invasive Fungal Infections Cooperative Group of the European Organization for Research and Treatment of Cancer and the Mycoses Study Group of the National Institute of Allergy and Infectious Diseases. The cumulative incidence (CI) of aspergillosis was calculated for the first episode of the infection that occurred within the specified time period after transplantation. To obtain an aggregate CI for each type of transplant, data from participating sites were weighted according to the proportion of transplants followed-up for specified time periods (four and 12 months for HSCT; six and 12 months for SOT). The aggregate CI of aspergillosis at 12 months was 0.5% after autologous HSCT, 2.3% after allogeneic HSCT from an HLA-matched related donor, 3.2% after transplantation from an HLA-mismatched related donor, and 3.9% after transplantation from an unrelated donor. The aggregate CI at 12 months was similar following myeloablative or non-myeloablative conditioning before allogeneic HSCT (3.1 vs. 3.3%). After HSCT, mortality at 3 months following diagnosis of aspergillosis ranged from 53.8% of autologous transplants to 84.6% of unrelated-donor transplants. The aggregate CI of aspergillosis at 12 months was 2.4% after lung transplantation, 0.8% after heart transplantation, 0.3% after liver transplantation, and 0.1% after kidney transplantation. After SOT, mortality at three months after diagnosis of aspergillosis ranged from 20% for lung transplants to 66.7% for heart and kidney transplants. The *Aspergillus* spp. associated with infections after HSCT included *A. fumigatus* (56%), *A. flavus* (18.7%), *A. terreus* (16%), *A. niger* (8%), and *A. versicolor* (1.3%). Those associated with infections after SOT included *A. fumigatus* (76.4%), *A. flavus* (11.8%), and *A. terreus* (11.8%). In conclusion, we found that invasive aspergillosis is an uncommon complication of HSCT and SOT, but one that continues to be associated with poor outcomes. Our CI figures are lower compared

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to those of previous reports. The reasons for this are unclear, but may be related to changes in transplantation practices, diagnostic methods, and supportive care.

Keywords aspergillosis, incidence, surveillance, transplantation

Introduction

Invasive aspergillosis has emerged as a leading cause of infection-related mortality among immunocompromised individuals, in particular among recipients of hematopoietic stem cell transplants (HSCT) or solid organ transplants (SOT). Aspergillosis has been estimated to occur after 6%–11% of HLA-matched related-donor allogeneic HSCT [1–3], and after 10.5% of HLA-mismatched or unrelated donor transplants [2]. Longitudinal studies have suggested that the incidence of *Aspergillus* infection increased among allogeneic HSCT recipients during the 1990s [2,4]. This finding has been attributed to the use of high-risk donor sources and more profound immunosuppression. Furthermore, several reports have described a shift towards a later onset of aspergillosis after transplantation, which might in part be associated with shorter periods of neutropenia after HSCT [1–3,5,6].

In autologous HSCT, the risk of invasive aspergillosis has been considered to be small when compared to allogeneic transplantation. Most reports have described an incidence of 1%–2%, or even less [7], although a higher incidence has been reported among patients who receive autologous grafts consisting of modified (CD34-selected) stem cells [8]. The time of onset after autologous transplantation is usually during the pre-engraftment period.

Among SOT recipients, the highest incidence of aspergillosis has been reported after lung transplantation (6%–13%), with heart and liver transplantation presenting a lower risk (1%–8%) [9–12]. More than half of the *Aspergillus* infections in liver transplant recipients now occur more than three months after transplantation [13]. In contrast, among heart transplant recipients, 72% of cases are diagnosed within the first three months after transplantation [14], while 50% of cases in lung transplant recipients occur within the first five months [12].

To date, most reports on the incidence of invasive fungal infections among different groups of transplant recipients have been derived from studies conducted in individual hospitals and may not be representative of the situation in other institutions. The Transplant Associated Infection Surveillance Network (TransNet) is a cooperative effort among academic institutions and the Centers for Disease Control and Prevention (CDC). It was established in 2000 with the objective of monitoring trends in the incidence of invasive fungal infections in recipients of organ transplants through a nationwide surveillance network of hospitals. By aggregating data from different sites, it was intended to develop estimates of the national incidence of these infections, to determine risk factors for different groups of transplant recipients, and to assess the impact of prevention programs. This report describes an interim analysis of data collected through TransNet with the objective of comparing current estimates of the incidence of invasive aspergillosis to those published elsewhere for different groups of HSCT and SOT recipients. To allow for comparisons with previous work, we used similar incidence calculation methods.

Methods

TransNet is based at the University of Alabama at Birmingham (UAB), and includes 25 hospitals throughout the United States that perform stem cell and/or solid organ transplants. The project began in March 2001 and continues to the present. All sites received local institutional review board approval before commencing enrollment of patients. The start date for surveillance differed from site to site.

Case definition and ascertainment

Cases of proven or probable invasive aspergillosis were defined according to the consensus definitions developed by the Invasive Fungal Infections Cooperative Group of the European Organization for Research and Treatment of Cancer and the Mycoses Study Group of the National Institute of Allergy and Infectious Diseases (EORTC-MSG) [15]. One limitation of these definitions that bears note is that they were developed for HSCT recipients or cancer patients and not SOT recipients. Transplant recipients with clinical signs consistent with aspergillosis, and histopathologic or microbiologic documentation of disease from biopsied tissues were considered to have 'proven' aspergillosis. Infection was considered 'probable' if cases had a positive culture and clinical and radiological signs

consistent with a diagnosis of aspergillosis. Cases with only 'possible' infection according to the EORTC-MSG consensus criteria were not included in this analysis. The day of diagnosis was the day on which the first diagnostic culture or examination was performed. For cases whose diagnosis was established during postmortem examination, the date of death was considered to be the day of diagnosis.

To detect cases at participating sites, investigators received information from attending physicians, participated in clinical rounds, and reviewed hospital records. Completeness of case ascertainment differed from site to site. Data were collected at each site using standardized forms and forwarded to the coordinating center (UAB). Information was collected on all transplants performed at each center (denominator data) and on all cases of invasive aspergillosis (numerator data). Each transplant procedure performed on an individual patient was counted as a separate transplant. The denominator data that were collected included the date of transplant and organ(s) transplanted. For those that received stem cell transplants, the type of transplant, relatedness of donor, HLA-matching status, and conditioning regimen were recorded. Each site also reported an assessment on all transplants at intervals after the transplant procedure. The information collected included the date of last evaluation at the site, or date of death (if known). The numerator data that were collected included site of infection, clinical signs, method of diagnosis, co-infections, co-morbid conditions, immunosuppressive regimens, and antifungal treatment. In addition, the outcome of the fungal infection at three months after diagnosis was recorded.

Microbiological methods

Cultures and histopathologic specimens were processed at the participating hospitals. Species identification was done with the routine methods in use at the participants' affiliated laboratories. All available fungal isolates were forwarded to UAB and then to the CDC for confirmation of identification.

Statistical analysis

For this analysis, we limited the cohort to those transplants that were conducted during the study period from 1 March 2001 through 31 December 2002, to maximize the likelihood of detecting all cases of aspergillosis that occurred during the 12 month period after transplantation.

For inclusion in the incidence calculation analysis, sites had to have provided numerator and denominator data for the study period. We calculated the 12 month site-specific cumulative incidence (CI) of invasive aspergillosis by including in the denominator all transplants performed during the study period, and by including in the numerator all first episodes of aspergillosis within the first 12 months after transplant. Because of the large proportion ($>20\%$) of transplants at some sites with inadequate follow-up at 12 months, we also calculated the four and six month site-specific CI of aspergillosis amongst HSCT and SOT, respectively. The proportion of transplants at each site for which follow-up was adequate at each specific time period was determined.

To obtain an aggregate CI for each type of transplant which better reflects the risk of aspergillosis, we pooled data among all sites. Because sites with a lower proportion of transplants with adequate follow-up were less likely to capture all cases, we weighted each site's contribution based on this proportion to calculate the aggregate CI. Survey methodology procedures were used to account for the cluster design.

The cumulative incidence of invasive aspergillosis among the different groups of HSCT recipients was estimated while accounting for the competing risks of infection-free death and re-transplantation [16]. Gray's k-sample test was used to determine if significant differences existed among the groups [17].

Results

Study population

During the 22-month study period, a total of 4489 patients underwent 4621 HSCT procedures, and 4059 patients underwent 4110 SOT procedures at the 19 TransNet sites that submitted transplant, assessment, and case data (Table 1). Among the autologous HSCT recipients, 6% had died from all causes four months after transplantation; 11% had died after 12 months. Among the allogeneic HSCT recipients, 20% had died after four months, and 35% after 12 months. Among the lung transplant recipients, 14% had died after six months, and 19% after 12 months.

Cumulative incidence after HSCT at individual sites

A total of 25 proven (35%) and 47 probable (65%) cases of invasive aspergillosis were diagnosed after HSCT. Table 2 summarizes the CI of aspergillosis, by HSCT type, at each participating site during the 12-month period after transplantation. At 12 of the 19 participating sites, there were no cases of aspergillosis after autologous HSCT; at the remaining sites, the CI values at four and 12 months ranged from 0.2% to 5.3% at both time points. With two exceptions (sites 8 and 9),

Table 1 Characteristics of transplants performed at the 19 participating sites, 1 March 2001 through 31 December 2002

Transplant type	No. of sites	No. of transplants performed:		Total
		Median	Range	
Autologous HSCT	19	103	19–523	2588
Allogeneic HSCT				
MRD	19	33	7–251	1216
MMRD	14	10	1–59	166
URD	18	20	1–137	651
MC*	16	36	3–243	1000
NMC*	16	14	1–119	512
Lung transplant	9	37	1–66	290
Liver transplant	11	81	45–197	1058
Heart transplant	10	18	11–73	349
Kidney transplant	11	166	58–537	2147
Other SOT	11	21	1–49	266

HSCT, hematopoietic stem cell transplant; MRD, matched related donor; MMRD, mismatched related donor; URD, unrelated donor; MC, myeloablative conditioning; NMC, nonmyeloablative conditioning.
*Information on conditioning regimen not available for 521 of 2033 allogeneic HSCT.

the CI values at both time points were identical, indicating that most *Aspergillus* infections in this group of transplants occur within the first four months after transplantation. The proportion of transplants with adequate follow-up at the participating sites ranged from 47% to 100% (median, 86%) at four months, and from 7% to 100% (median, 75%) at 12 months.

At four of the 19 participating sites, there were no cases of invasive aspergillosis after allogeneic HSCT (sites 5, 8, 12 and 16). One of these sites performed less than 10 allogeneic transplants during the study period, and a second performed less than 20 transplants. At the remaining 15 sites, the CI of aspergillosis ranged from 0.5% to 4.8% at 4 months, and from 1.0% to 7.9% at 12

Table 2 Incidence of invasive aspergillosis by participating site, for HSCT at 4 and 12 months after transplantation

Site	Autologous HSCT				Allogeneic HSCT			
	4 months		12 months		4 months		12 months	
	CI	%FU	CI	%FU	CI	%FU	CI	%FU
1	0	61	0	7	4.8	76	4.8	38
2	0.7	80	0.7	32	1.7	78	1.7	50
3	0	47	0	44	3.4	100	3.4	98
4	1.0	80	1.0	69	3.9	82	5.1	64
5	0	80	0	67	0	100	0	62
6	0.5	82	0.5	59	0.5	92	1.0	81
7	0	81	0	64	4.7	94	4.7	77
8	1.0	79	1.2	75	0	84	0	84
9	2.4	86	4.8	83	1.9	82	3.9	81
10	0	93	0	65	0	99	1.4	81
11	0	86	0	77	2.9	97	2.9	91
12	0	92	0	77	0	95	0	95
13	0	94	0	83	2.3	93	3.4	91
14	0	97	0	89	0.7	95	1.3	90
15	0	96	0	86	1.7	95	2.9	95
16	0	100	0	86	0	98	0	96
17	0.2	99	0.2	95	2.0	98	2.0	96
18	0	97	0	92	3.5	100	3.5	100
19	5.3	100	5.3	100	3.9	100	7.9	100

CI, cumulative incidence; %FU, proportion of transplants with adequate follow-up at specified time point.

Table 3 Incidence of invasive aspergillosis by participating site, for SOT at 6 and 12 months after transplantation

Site	Lung transplants				Kidney transplants				Other transplants			
	6 months		12 months		6 months		12 months		6 months		12 months	
	CI	%FU	CI	%FU	CI	%FU	CI	%FU	CI	%FU	CI	%FU
1	–	–	–	–	0	93	0	26	0	94	0	31
2	1.5	94	1.5	58	0	88	0	47	0.6	87	0.6	53
3	0	100	0	100	0	87	0	67	0.9	95	0.9	82
4	2.3	100	2.3	98	0	89	0	79	0.4	90	0.4	83
5	0	100	0	94	0	97	0	89	0	92	0	84
6	0	100	4.6	100	0	97	0	91	0.5	92	0.5	88
7	0	98	0	96	0.2	93	0.2	90	0.5	97	0.5	96
8	10.8	100	13.5	100	0.4	96	0.4	84	1.0	97	1.0	94
9	0	100	0	100	0	95	0	87	0	99	0	95
10	2.0	98	4.1	98	0	98	0	97	0	98	0	98
11	–	–	–	–	1.5	100	1.5	100	1.4	100	1.4	99

months. At seven sites, the CI of aspergillosis was identical at four and 12 months after transplantation; at three sites, the CI doubled between these time points. For allogeneic HSCT, the proportion of transplants with adequate follow-up at the participating sites ranged from 76% to 100% (median, 95%) at four months, and from 38 to 100% (median, 90%) at 12 months.

Cumulative incidence after SOT at individual sites

A total of 10 proven (50%) and 10 probable (50%) cases of invasive aspergillosis were diagnosed after SOT. Table 3 summarizes the CI of aspergillosis, by transplant type, at each of the 11 sites that performed SOT during the study period. One of the nine sites that performed lung transplantation had a CI of 10.8% after six months and 13.5% after 12 months. At four other sites, the CI at 12 months after this type of transplant ranged from 2.3% to 4.6%. The proportion of lung transplants with adequate follow-up at the nine sites ranged from 94% to 100% at 4 months, and from 58% to 100% (median, 98%) at 12 months.

No cases of invasive aspergillosis were diagnosed at eight of the 11 participating sites that performed kidney transplants. The CI values at the other three sites ranged from 0.2% to 1.5% at six and 12 months, indicating that the few cases of aspergillosis that occur in this group develop within 6 months of transplantation. The incidence of aspergillosis among recipients of other types of SOT was low, the CI values ranging from 0.4% to 1.4%.

Aggregate cumulative incidence

Table 4 summarizes the weighted aggregate incidence of proven or probable invasive aspergillosis at four and 12 months after autologous or allogeneic HSCT, and at six and 12 months after SOT. Overall, aspergillosis occurred in 0.5% of autologous and 2.9% of allogeneic HSCT during the first 12 months after transplantation. The infection was diagnosed in 2.3% of HLA-matched related-donor transplants, 3.2% of HLA-mismatched related-donor transplants, and 3.9% of unrelated-donor transplants. The aggregate CI of aspergillosis was similar following myeloablative or non-myeloablative conditioning before allogeneic transplantation (3.1% vs. 3.3% at 12 months, respectively). Overall, 0.1% of renal transplants, 0.3% of liver transplants, 0.8% of heart transplants, and 2.4% of lung transplants developed aspergillosis within 12 months after transplantation.

Fig. 1 suggests that there are differences, though not statistically significant, in the probability of developing invasive aspergillosis over the 12-month period after transplantation between the three different allogeneic HSCT groups ($P = 0.10$). There is a significant difference in the probability of developing *Aspergillus* infection between the autologous and allogeneic transplant groups ($P = < 0.01$). There is no significant difference ($P = 0.94$) in the probability of developing aspergillosis among allogeneic transplant recipients who received myeloablative versus non-myeloablative conditioning (Fig. 2).

Timing of infection

As shown in Table 5, 53.8% of cases of invasive aspergillosis after autologous HSCT developed within one month of transplantation, and only 15.4% developed more than four months after transplant. Among matched-related donor and unrelated donor allogeneic HSCT, 35.7% and 23.1% of cases, respectively, occurred

Table 4 Aggregate incidence of invasive aspergillosis after HSCT or SOT at the participating sites, 1 March 2001 through 31 December 2002

Transplant type	No. of transplants	No. of cases after:		Weighted aggregate incidence (95% CL):			
		4 or 6 months	12 months	4 or 6 months		12 months	
Autologous HSCT	2588	11	13	0.4	(0.1, 0.7)	0.5	(0.1, 0.9)
Allogeneic HSCT	2033	43	59	2.1	(1.4, 2.8)	2.9	(1.7, 4.0)
MRD	1216	18	28	1.5	(0.7, 2.3)	2.3	(0.7, 4.0)
MMRD	166	5	5	3.1	(0.3, 5.8)	3.2	(0.4, 6.0)
URD	651	20	26	3.0	(1.9, 4.2)	3.9	(2.5, 5.3)
MC*	1000	26	32	2.6	(1.6, 3.5)	3.1	(1.9, 4.3)
NMC*	512	10	16	2.0	(0.2, 3.8)	3.3	(0.4, 6.1)
Lung transplant	290	7	10	2.4	(0.0, 5.4)	3.5	(0.0, 7.3)
Liver transplant	1058	3	3	0.3	(0.0, 0.7)	0.3	(0.0, 0.7)
Heart transplant	349	3	3	0.8	(0.1, 1.6)	0.8	(0.1, 1.6)
Kidney transplant	2147	3	3	0.1	(0.0, 0.3)	0.1	(0.0, 0.3)
Other SOT	266	1	1	0.4	(0.0, 1.2)	0.4	(0.0, 1.2)

MRD, matched related donor; MMRD, mismatched related donor; URD, unrelated donor; MC, myeloablative conditioning; NMC, non-myeloablative conditioning.
*Information on conditioning regimen not available for 521 of 2033 allogeneic HSCT.

more than four months after transplantation. When grouped by conditioning regimen, 18.7% of cases of *Aspergillus* infection occurred more than four months following allogeneic HSCT with myeloablative conditioning compared with 37.5% of cases following non-myeloablative conditioning.

The numbers of cases of aspergillosis that occurred after SOT were small. Nonetheless, as shown in Table 6, it was noted that seven of the ten *Aspergillus* infections that developed in lung transplants did so within six months after transplantation, as did the cases that followed liver or heart transplantation. The three cases of invasive aspergillosis that occurred in kidney transplant recipients all occurred during the first month after transplantation.

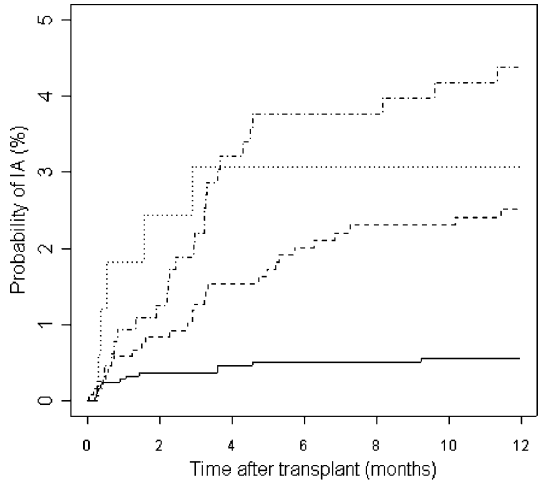

Fig. 1 Cumulative incidence of invasive aspergillosis (IA) among autologous HSCT recipients (–), allogeneic HSCT recipients who received grafts from matched related donors (--), mismatched related donors (···), or unrelated donors (–·–).

Mortality

The outcome at three months of aspergillosis presented here does not attempt to attribute the cause of mortality to the infection. Mortality among cases of aspergillosis ranged from 53.8% after autologous HSCT to 84.6% after unrelated-donor HSCT, at three

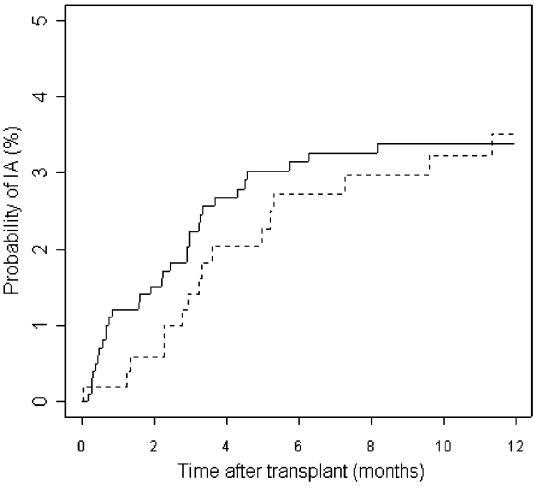

Fig. 2 Cumulative incidence of invasive aspergillosis (IA) among allogeneic HSCT recipients after myeloablative (-) or non-myeloablative conditioning (--).

Table 5 Time of diagnosis and mortality of invasive aspergillosis after HSCT at the participating sites, 1 March 2001 through 31 December 2002

Transplant type	No. (%) of cases diagnosed after:						No. (%) of deaths among cases[a]	
	0–1 month		2–4 months		5–12 months			
Autologous HSCT	7	(53.8)	4	(30.8)	2	(15.4)	7	(53.8)
Allogeneic HSCT	16	(27.1)	27	(45.8)	16	(27.1)	45	(76.3)
MRD	7	(25.0)	11	(39.3)	10	(35.7)	19	(67.8)
MMRD	3	(60.0)	2	(40.0)	0		4	(80.0)
URD	6	(23.1)	14	(53.8)	6	(23.1)	22	(84.6)
MC*	12	(37.5)	14	(43.8)	6	(18.7)	24	(75.0)
NMC*	1	(6.3)	9	(56.2)	6	(37.5)	12	(75.0)

[a]3 months after diagnosis of aspergillosis.
MRD, matched related donor; MMRD, mismatched related donor; URD, unrelated donor; MC, myeloablative conditioning; NMC, non-myeloablative conditioning.
*Information on conditioning regimen not available for 521 of 2033 allogeneic HSCT.

months following diagnosis of the infection (Table 5). Mortality among cases of aspergillosis ranged from 20% after lung transplantation to 66.7% after heart or kidney transplants (Table 6).

Etiologic agents

A total of 75 isolates were obtained from 72 cases of aspergillosis that occurred after HSCT; seven cases (10%) were due to multiple species. The *Aspergillus* spp. associated with these cases included *A. fumigatus* (56%), *A. flavus* (18.7%), *A. terreus* (16%), *A. niger* (8%), and *A. versicolor* (1.3%). Seventeen isolates were obtained from the 20 cases of aspergillosis among SOT recipients. These included *A. fumigatus* (76.4%), *A. flavus* (11.8%), and *A. terreus* (11.8%).

Discussion

This is the first report of the incidence of invasive aspergillosis to describe the occurrence of this infection among different groups of HSCT and SOT recipients in hospitals across the United States. Compared to prior studies, our CI figures are lower for both HSCT and SOT, despite using similar case definitions and comparable calculation methods.

The aggregate incidence of aspergillosis reported here ranged from 0.5% after autologous HSCT, to 3.9% after allogeneic transplantation from an unrelated donor (Table 4). To date, most published reports have described an incidence of 1%–2%, or even less, of invasive aspergillosis after autologous HSCT [7]. As has been reported elsewhere, more than 50% of *Aspergillus* infections in this patient group occurred within one month of transplantation (Table 5) and remain associated with very poor outcome (53.8% mortality at 3 months after diagnosis).

It is well recognized that some allogeneic HSCT recipients are at much greater risk of developing invasive aspergillosis than others, with recipients of unrelated donor transplants being at highest risk [1,2]. Our results for the aggregate incidence of aspergillosis after allogeneic HSCT ranged from 2.3% after transplantation from an HLA-matched related-donor, to

Table 6 Time of diagnosis and mortality of invasive aspergillosis after SOT at the participating sites, 1 March 2001 through 31 December 2002

Transplant type	No. (%) of cases diagnosed after:						No. (%) of deaths among cases[a]	
	0–1 month		2–6 months		7–12 months			
Lung transplant	2	(20.0)	5	(50.0)	3	(30.0)	2	(20.0)
Liver transplant	2	(66.7)	1	(33.3)	0		1	(33.3)
Heart transplant	1	(33.3)	2	(66.7)	0		2	(66.7)
Kidney transplant	3	(100)	0		0		2	(66.7)
Other SOT	1	(100)	0		0		0	

[a]3 months after diagnosis of aspergillosis.

3.9% after transplantation from an unrelated donor (Table 4). These figures are lower than those published elsewhere (6%–11%) [1–3]. As other groups have noted [1,2], 27.1% of cases of aspergillosis occurred more than four months after allogeneic HSCT. This suggests that the burden of risk has shifted from the neutropenic pre-engraftment phase of allogeneic HSCT to the post-engraftment phase where the immunosuppression of graft-versus-host disease is predominant, and T-cell function is still diminished. The outcome at three months of *Aspergillus* infection among this group of transplants was dismal, with a mortality rate of 76.3% (Table 5).

Results of several small single-center studies have suggested that patients who undergo allogeneic HSCT after non-myeloablative conditioning are at lower risk of developing invasive fungal infections than those receiving conventional allogeneic HSCT [18,19]. In other recent reports, however, non-myeloablative allogeneic HSCT transplantation has been associated with similar rates of invasive aspergillosis than conventional myeloablative HSCT [20,21]. Our results indicate that the risk of developing aspergillosis was similar in both groups (Table 4; Fig. 2). This suggests that differences in conditioning regimens are less likely to account for site-specific differences in incidence compared to the impact of differences in donor selection. However, data on the conditioning regimen were not provided for 521 of 2033 allogeneic stem cell transplants (26%) and some misclassification of the remainder could have biased any differences observed.

Among SOT recipients, the highest incidence of aspergillosis was detected after lung transplantation (3.5%), with other types of transplantation presenting a lower risk (Table 4). Despite the high rates of long-term follow-up ($>$90% at 8 of 9 sites), our results for lung transplants are lower than those previously reported (6%–13%) [9,11,12]. As has been noted elsewhere, more than 50% of *Aspergillus* infections in this patient group occurred within six months after transplantation [12]. Too few cases of aspergillosis were detected among other groups of SOT recipients to confirm recent reports regarding the timing or mortality rates of these infections after transplantation. The mortality rate (20%) we observed among lung transplant recipients with *Aspergillus* infection is low compared to some other recent reports (50%–52%) [11,12]. The reasons for this are unclear.

Traditional measures of the CI of aspergillosis after HSCT and SOT include all transplants performed during the study period in the denominator, without taking into account the length of follow-up time after transplantation. However, a number of *Aspergillus* infections occur several months after transplantation, and are often diagnosed and treated at hospitals distant from the original transplant site. These cases would not be captured in the numerator of the incidence calculation. The larger the proportion of transplant recipients without adequate follow-up at a participating site, the greater the likelihood that cases with later onset will be missed and this in turn will result in an underestimation of the true site-specific incidence. To address this issue, we calculated four and six month CI figures. This increases the likelihood that most cases of aspergillosis would be captured, since most cases occur during this shorter time period and most transplant recipients are followed up to these dates.

Many factors could account for the differences in site-specific incidence rates reported here (Tables 2 and 3). In addition to variations in rates of follow-up, variations in diagnostic methods and practices between sites will result in different thresholds for the initiation of antifungal treatment. The nature and timing of both diagnostic tests and therapeutic interventions will affect the likelihood of transplant recipients meeting the diagnostic criteria for proven or probable aspergillosis required for inclusion as a case in this surveillance. Furthermore, our analysis of the aggregated surveillance data shows that transplant-related factors, such as donor type, can affect site-specific CI. Other host-related factors (e.g., underlying disease prompting transplant, comorbid conditions, etc.), and other transplant-related factors (e.g. stem cell type, transplantation conditioning and post-transplantation immunosuppression, etc.), may also impact the incidence of *Aspergillus* infection at the individual sites.

To account for inter-site variations in follow-up and donor type, we calculated aggregate CI figures for aspergillosis by weighting each site according to its completeness of follow-up, and reported the aggregate incidence by donor type and conditioning regimen. Extrapolating our incidence estimates to other transplant centers in the United States and elsewhere must be done with caution for the reasons outlined above. In addition, it should be noted that the sample of participating sites was not randomly selected, but rather was a convenience sample.

A. fumigatus remains the most frequent cause of invasive aspergillosis. However, at least 30 other species, including *A. flavus, A. terreus, A. niger, A. nidulans*, and *A. versicolor* have been reported to cause human infection [22]. In some centers, *A. terreus* has emerged as a cause of aspergillosis [23–25]. This species is of concern because it is less susceptible to amphotericin B in vitro and in vivo than *A. fumigatus* [26,27] and has the potential to cause fulminant invasive infections in

immunocompromised patients [23–25]. In this study, *A. fumigatus* was the most frequent etiologic agent, but *A. terreus* accounted for 16% of cases of invasive aspergillosis in HSCT recipients, and 11.8% of cases in SOT recipients.

In conclusion, TransNet is the first national surveillance program to estimate the risk of invasive aspergillosis among transplant recipients. We identified many challenges for aggregated national data with this interim analysis. Overall, we found that invasive aspergillosis is an uncommon complication of HSCT and SOT, but one that continues to be associated with poor outcomes. Many factors could account for the lower incidence of invasive aspergillosis noted here, including changes in transplantation practices, diagnostic methods, and supportive care. Whether the lower incidence reflects a true decrease or an underestimate will require further investigation in longitudinal studies.

Appendix

In addition to the authors, members of the TransNet investigators group were as follows: B.D. Alexander (Durham, NC); E.J. Anaissie (Little Rock, AR), D.R. Andes (Madison, WI), J. Brown (Stanford, CA), L.M. Brumble (Jacksonville, FL), A. Freifeld (Omaha, NE), L.A. Herwaldt (Iowa City, IA), J. Ito (Los Angeles, CA), C.A. Kauffman (Ann Arbor, MI), K.M. Knapp (Memphis, TN), J.E. Mangino (Columbus, OH), V.A. Morrison (Minneapolis, MN), G. Papanicolau (New York, NY), T.F. Patterson (San Antonio, TX), T.M. Perl (Baltimore, MD), L. Polish (St. Louis, MO), M. Schuster (Philadelphia, PA), J. Somani (Atlanta, GA), R.C. Walker (Rochester, MN), J.R. Wingard (Gainesville, FL).

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