MAJOR ARTICLE

Fungal Infections in Recipients of Hematopoietic Stem Cell Transplants: Results of the SEIFEM B-2004 Study—Sorveglianza Epidemiologica Infezioni Fungine Nelle Emopatie Maligne

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Background. The purpose of our study was to evaluate the incidence and outcome of invasive fungal infection (IFI) among patients who underwent autologous or allogeneic hematopoietic stem cell transplantation (HSCT) at 11 Italian transplantation centers.

Methods. This cohort-retrospective study, conducted during 1999–2003, involved HSCT patients admitted to 11 tertiary care centers or university hospitals in Italy, who developed IFIs (proven or probable).

Results. Among 3228 patients who underwent HSCT (1249 allogeneic HSCT recipients and 1979 autologous HSCT recipients), IFI occurred in 121 patients (overall incidence, 3.7%). Ninety-one episodes (2.8% of all patients) were due to molds, and 30 (0.9%) were due to yeasts. Ninety-eight episodes (7.8%) occurred among the 1249 allogeneic HSCT recipients, and 23 (1.2%) occurred among the 1979 autologous HSCT recipients. The most frequent etiological agents were *Aspergillus* species (86 episodes) and *Candida* species (30 episodes). The overall mortality rate was 5.7% among allogeneic HSCT recipients and 0.4% among autologous HSCT recipients, whereas the attributable mortality rate registered in our population was 65.3% (72.4% for allogeneic HSCT recipients and 34.7% for autologous HSCT recipients). Etiology influenced the patients' outcomes: the attributable mortality rate for aspergillosis was 72.1% (77.2% and 14.3% for allogeneic and autologous HSCT recipients, respectively), and the rate for *Candida* IFI was 50% (57.1% and 43.8% for allogeneic and autologous HSCT recipients, respectively).

Conclusions. IFI represents a common complication for allogeneic HSCT recipients. *Aspergillus* species is the most frequently detected agent in these patients, and aspergillosis is characterized by a high mortality rate. Conversely, autologous HSCT recipients rarely develop aspergillosis, and the attributable mortality rate is markedly lower. Candidemia was observed less often than aspergillosis among both allogeneic and autologous HSCT recipients; furthermore, there was no difference in either the incidence of or the attributable mortality rate for candidemia among recipients of the 2 transplant types.

Invasive fungal infection (IFI) is a growing cause of morbidity and mortality among patients with hematologic malignancies, particularly in those affected by acute myeloid leukemia [1–5] and in persons who undergo hematopoietic stem cell transplantation (HSCT) [6–18]. Although attention has mainly focused on identifying risk or prognostic factors in HSCT recipients [6, 7, 19, 20], few attempts have been made to assess the real incidence of IFI (table 1) [6–18].

Recent reports, which have mainly been based on

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autopsy data, have revealed a progressive increase in the overall incidence of IFI, particularly those caused by molds, and there has been an increasing number of episodes of IFI due to *Aspergillus* species other than *Aspergillus fumigatus,* to *Fusarium* species, and to *Zygomycetes* species [13, 21–23]. This change in epidemiological trends may be related not only to a real increase in the number of IFI episodes due to these emerging pathogens, but also to more-accurate diagnostic tools, which reduce the probability of misdiagnosis, or to prior widespread administration of fluconazole prophylaxis, which provides coverage against many *Candida* strains but not against *Aspergillus* species or other molds [6].

The risk for IFI after HSCT depends on the graft source (i.e., peripheral stem cells, bone marrow, or cord blood), the presence of acute or chronic graft-versus-host disease (GVHD), administration of steroids, the presence of cytomegalovirus (CMV) disease, and eventual antifungal prophylaxis [24, 25]. The risk of IFI is greater among allogeneic HSCT recipients, among whom the incidence of proven or probable IFI is reported to be in the range of 5%–18% [8–16], compared with 0%–1.1% [9–12], even after $CD34^+$ selection, among autologous HSCT recipients (table 1) [26]. Despite identification of these risk factors, the incidence of IFI is probably underestimated in the context of transplantation, because an unknown number of patients die without the pathogen being identified [27, 28], and mortality rate data are frequently based on meta-analyses [20].

In the present study, we investigated the current incidence of IFI and IFI-related mortality rates among inpatients who underwent autologous or allogeneic HSCT during 1999–2003 in Italian transplantation centers.

PATIENTS AND METHODS

We performed a retrospective study in 11 tertiary care centers or university hospitals in Italy to assess the incidence of IFI

Table 1. Incidence of candidemia and aspergillosis and related mortality in transplant recipients.

Condition, study	Year(s)	No. of included subjects	No. (%) of cases of IFI	AMR[a]
Candidemia and allogenic HSCT				
Marr et al. [6]	1994–1997	655	30 (4.5)	6 (20)
Martino et al. [7]	1996–2000	395	12 (3)	1
Jantunen et al. [8]	1990–2001	1188	7 (0.6)	3/6 (50)[b]
Aspergillosis				
Autologous HSCT				
Grow et al. [9]	1997–1998	149	0 (0)	0 (0)
Cornet et al. [10]	1994–1998	NR	23 (1.1)	NR
Jantunen et al. [8]	1990–2001	1188	9 (0.8)[c]	2/7 (36)[b]
Morgan et al. [11]	2001–2002	2588	13 (0.5)	7 (53.8)
Zaoutis et al. [12]	2000	822	3 (0.3)	2 (66)
Allogenic HSCT				
Baddley et al. [13]	1997–1998	94	15 (16)[d]	17 (87)
Marr et al. [14]	1985–1999	5589	375 (6.7)[d]	…[e]
Martino et al. [7]	1996–2000	395	32 (8.1)	22 (59)
Cornet et al. [10]	1994–1998	NR	199 (12.8)	NR
Grow et al. [9]	1997–1998	93	14 (15.1)	5 (36)
Fukuda et al. [15]	1997–2001	163	25 (15)	14 (56)
Kojima et al. [16]	NR	664[f]	35 (5.3)	NR
Morgan et al. [11]	2001–2002	2033	50 (2.9)	45 (76.3)
Zaoutis et al. [12]	2000	2219	101 (4.5)	45 (45)

NOTE. AMR, attributable mortality rate; HSCT, hematopoietic stem cell transplantation; IFI, invasive fungal infection; NR, not reported.

[a] Data are no. (%) of patients or proportion of patients (%), unless otherwise indicated.

[b] One patient with candidemia and 2 patients with aspergillosis were not treated, and their outcomes were not reported.

[c] Two additional infections due to molds (one due to *Fusarium* species and the other due to *Mucor* species) were observed.

[d] Includes infections also due to other molds.

[e] AMR was 70%–80%.

[f] A total of 486 patients underwent conventional HSCT, and 178 underwent reduced-intensity HSCT.

Table 2. Characteristics of 121 patients with invasive fungal infection (IFI).

Characteristic	All patients	HSCT type, IFI cause			
		Allogenic		Autologous	
		Mold	Yeast	Mold	Yeast
No. (%) of patients	121 (100)	84 (100)	14 (100)	7 (100)	16 (100)
Age, median years (range)	42 (16–70)	41 (16–70)	38 (16–57)	49 (35–63)	53 (25–65)
Ratio of male to female patients	1.7:1	1.8:1	1:1	6:1	1.3:1
Underlying hematological disease					
Acute myeloid leukemia	49 (40.5)	37 (44)	6 (43)	1 (14)	5 (31)
Acute lymphoid leukemia	24 (20)	18 (21)	4 (29)	2 (29)	0 (0)
Chronic myeloid leukemia	9 (7.5)	8 (9)	1 (7)	0 (0)	0 (0)
Chronic lymphoid leukemia	5 (4)	3 (4)	0 (0)	1 (14)	1 (6)
Non-Hodgkin lymphoma	10 (8.5)	4 (5)	0 (0)	2 (29)	4 (25.5)
Hodgkin disease	4 (3)	3 (4)	0 (0)	0 (0)	1 (6)
Multiple myeloma	15 (12.5)	8 (9)	2 (14)	1 (14)	4 (25.5)
Severe aplastic anemia	5 (4)	3 (4)	1 (7)	0 (0)	1 (6)
Underlying disease phase at transplantation					
Complete remission	60 (49.5)	37 (44)	10 (71)	5 (71)	8 (50)
Not in remission	61 (50.5)	47 (56)	4 (29)	2 (29)	8 (50)
Conditioning regimen					
Chemotherapy only	…	49 (58)	11 (79)	…	…
Combined chemotherapy and TBI	…	35 (42)	3 (21)	…	…
Donor					
HLA-matched, related	…	59 (70)	10 (71)	…	…
HLA-mismatched, related	…	6 (7)	0 (0)	…	…
HLA-matched, unrelated	…	19 (23)	4 (29)	…	…
Stem cell source					
Bone marrow	53 (44)	41 (49)	7 (50)	3 (43)	2 (12.5)
Peripheral blood	64 (53)	39 (46)	7 (50)	4 (57)	14 (87.5)
Umbilical cord blood	4 (3)	4 (5)	0 (0)	0 (0)	0 (0)
Site of infection					
Lung	68 (56)	62 (74)	0 (0)	6 (86)	0 (0)
Blood	33 (27)	3 (4)	14 (100)	0 (0)	16 (100)
CNS	3 (2.5)	3 (4)	0 (0)	0 (0)	0 (0)
Sinus	3 (2.5)	3 (4)	0 (0)	0 (0)	0 (0)
Disseminated	14 (12)	13 (14)	0 (0)	1 (14)	0 (0)
Antimycotic prophylaxis					
Oral polyenes only	29 (24)	13 (15)	8 (57)	3 (43)	5 (31)
Systemic					
Fluconazole	47 (39)	36 (43)	4 (29)	4 (57)	3 (19)
Itraconazole	25 (21)	15 (18)	2 (14)	0 (0)	8 (50)
Liposomal amphotericin B	10 (8)	10 (12)	0 (0)	0 (0)	0 (0)
Voriconazole	6 (5)	6 (7)	0 (0)	0 (0)	0 (0)
Other[a]	4 (3)	4 (5)	0 (0)	0 (0)	0 (0)
Onset of IFI					
≤100 days after transplantation	…	54 (64)	7 (50)	…	…
>100 days after transplantation	…	30 (36)	7 (50)	…	…
GVHD					
Acute	56 (46)	52 (62)	4 (29)	…	…
Chronic	41 (34)	37 (44)	4 (29)	…	…
CMV serologic test result					
Positive	…	47 (56)	6 (43)	…	…
Negative	…	37 (44)	8 (57)	…	…
CVC in place					
Yes	104 (86)	74 (88)	11 (79)	3 (43)	16 (100)
No	17 (14)	10 (12)	3 (21)	4 (57)	0 (0)

NOTE. CVC, central venous catheter; CMV, cytomegalovirus; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; TBI, total body irradiation.

[a] Amphotericin B deoxycholate or amphotericin B lipid complex.

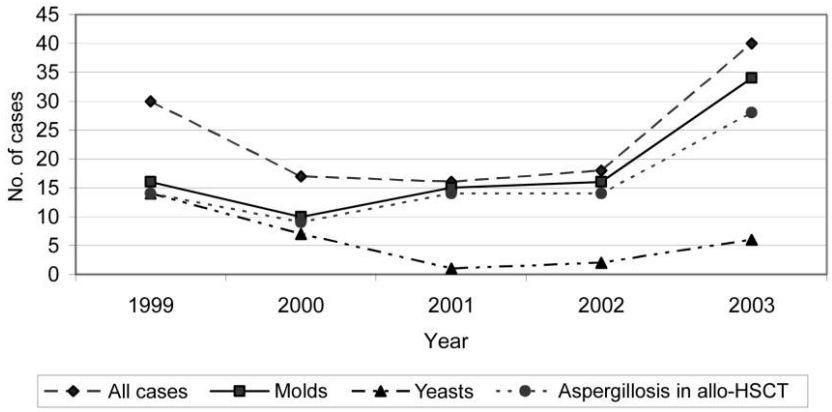

Figure 1. Annual incidence of invasive fungal infections—in particular, of invasive aspergillosis in allogenic hematopoietic stem cell transplant (allo-HSCT) recipients—during the study period.

among adult HSCT recipients. Enrollment was limited to patients undergoing autologous or allogenic HSCT during the period from January 1999 through December 2003.

The European Organisation for Research and Treatment of Cancer/Mycosis Study Group consensus criteria were used to define IFI [29], with modification made for additional diagnostic tools, such as the galactomannan test. Only infections that were classified as proven or probable were included in the data analysis.

Study design. Each transplantation center completed a questionnaire eliciting the following data: the number of allogeneic and autologous HSCTs performed during 1999–2003 at each center, the stem cell source (i.e., bone marrow, peripheral blood, or umbilical cord) for each transplantation, and data on all IFI episodes experienced by HSCT recipients. For each patient, we requested the following information: age, sex, disease and disease stage at time of HSCT, type of HSCT (autologous or allogeneic), type of graft (from a matched, related donor; matched, unrelated donor; or a mismatched, related donor), conditioning regimen, presence or absence of a central venous catheter, CMV serologic data, presence of acute or chronic GVHD, history of fungal infection, receipt of antifungal prophylaxis, diagnostic evaluation findings, date of IFI diagnosis, time from HSCT to diagnosis of IFI, fungal species isolated, in vivo and postmortem microbiological and histological findings, and outcome (assessed on the 150th day after IFI diagnosis).

In each participating center, antifungal prophylaxis consisted of itraconazole or fluconazole in addition to local agents. Transplantation centers did not change their guidelines during the study period. Similar therapeutic protocols that reflected the current guidelines of the Infectious Diseases Society of America [30, 31] were used by all centers throughout the study.

Multiple IFI episodes in any individual patient were counted as separate infections unless they were caused by the same pathogen. Overall and IFI attributable mortality rates (AMRs) were estimated. For each patient, a correct analysis of any condition that could have contributed to death was required from attending physicians; the IFI AMR was finally defined as a progression of sepsis-related symptoms or of involved organ

Table 3. Attributable mortality rate and overall mortality rate for all types of invasive fungal infection (IFI) among transplant recipients.

		Aspergillus IFI			IFI due to other molds[a]			*Candida* IFI		
Transplantation type	No. of patients	No. (%) of cases	Death[b]	Overall mortality	No. (%) of cases	Death[b]	Overall mortality	No. (%) of cases	Death[b]	Overall mortality
Allogenic HSCT										
Patients, cases, or deaths	1249	79 (92)	61	…	5 (100)	2	…	14 (47)	8	…
Rate, % (95% CI)	…	…	77.2 (67.0–85.5)	4.9 (3.8–6.2)	…	40 (7.3–81.8)	0.2 (0.03–0.5)	…	57.1 (31.1–80.4)	0.6 (0.3–1.2)
Autologous HSCT										
Patients, cases, or deaths	1979	7 (8)	1	…	0	…	…	16 (53)	7	…
Rate, % (95% CI)	…	…	14.3 (0.7–53.0)	0.1 (0.002–0.2)	…	…	…	…	43.8 (21.5–68.0)	0.4 (0.2–0.7)
Total										
Patients, cases, or deaths	3228	86 (100)	62	…	5 (100)	2	…	30 (100)	15	…
Rate, % (95% CI)	…	…	72.1 (61.9–80.8)	1.9 (1.5–2.4)	…	40 (7.3–81.8)	<0.1 (0.001–0.2)	…	50 (32.5–67.5)	0.5 (0.3–0.7)

NOTE. HSCT, hematopoietic stem cell transplantation.

[a] *Fusarium* species, 3 cases; *Scedosporium* species, 1 case; and *Mucor* species, 1 case.

[b] Data are no. of deaths or attributable mortality rate.

Table 4. Incidence of invasive fungal infection and attributable mortality rate (AMR) among recipients of allogenic hematopoietic stem cell transplants from different types of donors.

Transplant donor	No. (%) of patients	No. of cases	No. of deaths
Matched, related			
Patients, cases, or deaths	747 (60)	69	49
Incidence or AMR, % (95% CI)[a]	…	9.2 (7.3–11.5)	71 (59.5–80.8)
Mismatched, related			
Patients, cases, or deaths	181 (14)	6	5
Incidence or AMR, % (95% CI)[a]	…	3.3 (7.3–11.5)	83 (40.9–99.2)
Matched, unrelated			
Patients, cases, or deaths	321 (26)	23	17
Incidence or AMR, % (95% CI)[a]	…	7.1 (7.3–11.5)	74 (53.4–88.7)
Total			
Patients, cases, or deaths	1249 (100)	98	71
Incidence or AMR, % (95% CI)[a]	…	7.8 (7.3–11.5)	72 (63.0–80.6)

[a] Rate is the incidence for no. of cases and AMR for no. of deaths.

failure in the absence of other comorbid conditions believed to cause death.

Statistical analysis. Univariate analysis, which was performed using the χ^2 test, and multivariate analysis, which was determined using logistic regression analysis, identified variables predicting mortality. Independent variables tested in the univariate analysis included sex, age group (16–35, 36–49, and >50 years), autologous or allogeneic HSCT, source of stem cells (peripheral blood, bone marrow or umbilical cord), $CD34^+$ selection, disease (acute myeloid leukemia, acute lymphoid leukemia, chronic myeloid leukemia, chronic lymphoid leukemia, non-Hodgkin lymphoma, Hodgkin disease, multiple myeloma, and severe aplastic anemia), complete remission at transplantation, presence or absence of a central venous catheter, time to IFI after transplantation, site of infection, pathogen (mold or yeast), antifungal prophylaxis (local or systemic), prophylactic agent (fluconazole, itraconazole, voriconazole, and/or liposomal amphotericin B), and center in which the patient was observed. For allogeneic HSCT, we also analyzed the type of graft (from a matched, related donor; a matched, unrelated donor; or a mismatched, related donor), use of total body irradiation as part of the patient's conditioning regimen (yes or no), presence or absence of acute or chronic GVHD, and CMV serologic test results. Variables with incomplete data sets were not included.

Multivariate analysis was performed using a logistic regression model in which goodness of fit was assessed with the Hosmer and Lemeshow test [32]. The model included only variables with a univariate P value <.25, applying the stepwise-with-backward-elimination method. Adjusted ORs and 95% CIs were calculated.

We repeated the univariate and the multivariate analyses after stratification based on type of graft (allogeneic vs. autologous HSCT) and pathogen (molds vs. yeasts). Furthermore, aspergillosis was analyzed only in allogeneic HSCT recipients. Statistical significance was set at $P < .05$. The analysis was performed using SPSS software for Windows, version 13.0 (SPSS).

RESULTS

During the 5-year study, 3228 patients underwent HSCT at 11 transplantation centers (1979 underwent autologous HSCT, and 1249 underwent allogeneic HSCT). One hundred twenty-one episodes of IFI (incidence, 3.7%; 95% CI, 3.1%–4.4%) were documented; 59 (49%) were proven cases, and the others were considered to be probable infections. The clinical characteristics of the patients are reported in table 2. The overall incidence of IFI increased during the study period, particularly from 2002 to 2003 (relative risk [RR], 2.24; 95% CI, 1.29–3.87; $P = .003$) (figure 1). Molds were responsible for 91 proven and probable episodes (incidence, 2.8%; 95% CI, 2.3%–3.4%), and yeasts were responsible for 30 proven episodes (incidence, 0.9%; 95% CI, 0.6%–1.3%). The lung was the most frequently affected site with regard to *Aspergillus* infection (68 cases). Mold infections disseminated to multiple sites in 14 cases (table 2). Sepsis occurred in 33 patients; 30 cases were due to *Candida* species, and 3 were due to *Fusarium* species.

The overall mortality rate for IFI was 2.4% (79 of 3228 patients; 95% CI, 2.0%–3.0%), and the overall IFI AMR was 65.3% (79 of 121 cases; 95% CI, 56.5%–73.4%), with significant differences when we compared mold and yeast infections (table 3): the aspergillosis AMR was significantly higher than the candidemia AMR (72.1% vs. 50%; $P = .043$). Infections with molds other than *Aspergillus* species were associated with a low AMR (40%; 95% CI, 7.3%–81.8%). The aspergillosis AMR varied during the study period, decreasing (albeit not significantly) from 81% in 1999 to 59% in 2003 (RR, 0.73; 95% CI, 0.50–1.06; $P = .12$).

Univariate analysis revealed that the following parameters had no significant influence on outcome: age, sex, disease, transplantation center, complete remission at transplantation, stem cell source, site of infection, presence of a central venous catheter, and receipt of systemic prophylaxis with fluconazole, itraconazole, liposomal amphotericin B, or voriconazole. Variables that negatively influenced outcome were allogeneic HSCT versus autologous HSCT (mortality rate, 72% vs. 35%; $P = .001$), mold infection versus yeast infection (mortality rate, 70% vs. 50%; $P = .043$), and systemic antifungal prophylaxis versus topical prophylaxis (mortality rate, 71% vs. 48%; $P = .027$). Multivariate analysis confirmed that allogeneic HSCT was associated with a worse prognosis than was autologous HSCT (OR, 4.64; 95% CI, 1.74–12.38; $P < .01$).

Allogeneic HSCT. Among recipients of allogeneic HSCTs, an HLA-matched, related donor was the source of stem cells in 747 (60%) of 1249 transplantations. HLA-mismatched, related donors or matched, unrelated donors were the sources for 181 patients (14%) and 321 patients (26%), respectively.

Table 5. Species distribution for invasive fungal infections (IFIs) in allogenic and autologous hematopoietic stem cell transplant (HSCT) recipients.

Cause of IFI	All patients		Allogenic HSCT recipients		Autologous HSCT recipients	
	No. of cases	Incidence, % (95% CI)	No. of cases	Incidence, % (95% CI)	No. of cases	Incidence, % (95% CI)
Molds						
All	91	2.8 (2.3–3.4)	84	6.7 (5.4–8.2)	7	0.4 (0.2–0.7)
Aspergillus species						
All	86	2.7	79	6.3	7	0.4
Unknown species	53	1.6	50	4	3	0.2
Aspergillus fumigatus	19	0.6	16	1.3	3	0.2
Aspergillus niger	5	0.2	4	0.3	1	0.1
Aspergillus terreus	5	0.2	5	0.4	0	…
Aspergillus flavus	4	0.1	4	0.3	0	…
Zygomycetes species	1	<0.1	1	0.1	0	…
Fusarium species	3	0.1	3	0.2	0	…
Scedosporium species	1	<0.1	1	0.1	0	…
Yeasts						
All	30	0.9 (0.6–1.3)	14	1.1 (0.6–1.8)	16	0.8 (0.5–1.3)
Candida species						
All	30	0.9	14	1.1	16	0.8
Candida albicans	13	0.4	7	0.6	6	0.3
Candida glabrata	5	0.2	0	…	5	0.3
Candida guillermondii	4	0.1	3	0.2	1	<0.1
Candida krusei	4	0.1	1	0.1	3	0.1
Candida parapsilosis	2	<0.1	1	0.1	1	<0.1
Candida tropicalis	1	<0.1	1	0.1	0	…
Candida zeylanoides	1	<0.1	1	0.1	0	…

Seven patients had experienced a fungal infection (probable aspergillosis) before transplantation.

Among the allogeneic HSCT recipients, 98 proven or probable IFIs were documented (incidence, 7.8%; 95% CI, 6.5%–9.4%). Most cases occurred among recipients of transplants from matched, related donors (table 4). As for the underlying hematological malignancies, acute lymphoid or myeloid leukemia were associated with the highest risk (66% of all cases). Most cases of IFI infection (61 [62%] of 98) occurred in the first 100 days after transplantation; 84 cases (86%) were due to molds, and 14 (14%) were due to yeasts. The majority of mold infections (79 [94%] of 84) were caused by *Aspergillus* species. The species was identified in 36% of *Aspergillus* isolates; *A. fumigatus* was the most common pathogen (16 of 84 episodes) (table 5). *Zygomycetes* and *Scedosporium* species were each responsible for 1 episode of IFI, and *Fusarium* species were responsible for 3. A significant increase in the annual incidence of aspergillosis was observed during the study period (RR, 2.47; 95% CI, 1.19–5.13; $P = .01$) (figure 1).

All yeast infections were caused by *Candida* species (14 episodes), as diagnosed by blood culture. *Candida albicans* was the etiologic agent in 7 episodes, and non-*albicans* species of *Candida* were responsible for the other 7 episodes.

The overall mortality rate for fungal infection was 5.7% (95% CI, 4.5%–7.1%), with an IFI AMR of 72% (95% CI, 63.0%–80.6%; 71 deaths among 98 cases of proven or probable IFI). The overall rate of mortality due to aspergillosis was 4.9% (95% CI, 3.8%–6.2%), with an *Aspergillus* infection AMR of 77.2% (95% CI, 67.0%–85.5%; 61 deaths among 79 cases of proven or probable *Aspergillus* infection). Two of the 3 *Fusarium* infections were fatal, as was the infection caused by *Zygomycetes* species. The patient who had *Scedosporium* infection survived. The overall rate of mortality due to *Candida* infection was 0.6% (95% CI, 0.3%–1.2%), with a *Candida* infection AMR of 57% (95% CI, 31.1%–80.4%; 8 deaths among 14 episodes of *Candida* infection). There were no differences in the AMRs for *C. albicans* infection (4 of 7 cases were fatal) and non-*albicans* *Candida* infection (4 of 7 cases were fatal).

Among the 98 patients with IFI, the majority received both oral polyenes and systemic antifungal drugs, particularly azoles. Distribution of fungal agents did not vary among topical or systemic prophylaxis recipients. At one transplantation center,

Table 6. Results of multivariate analysis for aspergillosis in allogenic hematopoietic stem cell transplant recipients (79 cases).

Variable	OR (95% CI)	*P*
Prophylaxis with fluconazole[a]		
Administered	1.00	
Not administered	1.16 (0.23–5.82)	.85
Time from transplantation to onset of infection		
⩽100 days	1.00	
>100 days	0.70 (0.17–2.92)	.62
Sex		
Male	1.00	
Female	2.27 (0.52–9.93)	.28
Previous infection		
No	1.00	
Yes	0.39 (0.07–2.06)	.27
Histological tests		
Performed	1.00	
Not performed	3.96 (0.65–24.04)	.14
Total body irradiation		
Yes	1.00	
No	0.14 (0.03–0.62)	**<.01**
Age, years		
16–35	1.00	
36–49	5.20 (1.12–24.07)	**.03**
>50	5.67 (1.00–32.04)	**.05**
Type of allograft donor		
Matched, related	1.00	
Mismatched, related	6.46 (0.37–111.64)	.20
Matched, unrelated	12.74 (1.20–134.69)	**.03**
CVC		
Absent	1.00	
Present	10.83 (1.62–72.25)	**.01**

NOTE. Statistically significant *P* values are shown in boldface. CVC, central venous catheter.

[a] This was the only significant parameter at univariate analysis.

6 breakthrough cases of aspergillosis occurred while voriconazole was being administered as secondary antifungal prophylaxis. All of these patients had received antifungal treatment during a previous therapeutic phase because of the occurrence of IFI before the HSCT procedure (1 proven, 2 probable, and 3 possible IFIs).

Systemic prophylaxis was associated with a significantly higher mortality rate (78% vs. 52%; $P = .02$), as confirmed by multivariate analysis (OR, 4.89; 95% CI, 1.53–15.60; $P = .01$). The AMR was higher in patients whose hematological malignancy was not in complete remission at the time of transplantation (80% vs. 64%; $P = .067$). More patients died of fungal infection during the first 100 days after transplantation (79%, compared with 62% for ⩾101 days after transplantation; $P = .076$).

Univariate analysis was performed for aspergillosis in allogeneic HSCT recipients alone (79 cases) and revealed that fluconazole prophylaxis was negatively correlated with outcome ($P = .042$). Patients who underwent total body irradiation in the conditioning regimen had a better prognosis ($P = .03$). Multivariate analysis confirmed this finding and indicate that the following variables influenced outcome: age >36 years, presence of a central venous catheter, and receipt of a transplant from a matched, unrelated donor (table 6).

Autologous HSCT. Among patients who underwent autologous HSCT, 23 proven or probable IFIs were documented; 7 were due to molds, and 16 were due to yeasts. The overall incidence was estimated to be 1.2% (95% CI, 0.08%–1.7%). Mold infections were all caused by *Aspergillus* species, whereas yeast infections were all caused by *Candida* species. The agent was *C. albicans* in 6 episodes (33%) and non-*albicans* species of *Candida* in 10 episodes (67%).

Table 7. Onset of fungal infection in allogenic and autologous hematopoietic stem cell transplant (HSCT) recipients.

Cause of infection, transplantation type	Time of onset after transplantation, no. (%) of patients		*P*
	⩽100 days	>100 days	
Yeasts			**.001**
Allogenic HSCT	7 (50)	7 (50)	
Autologous HSCT	16 (100)	0 (0)	
Molds			.09
Allogenic HSCT	54 (64)	30 (36)	
Autologous HSCT	7 (100)	0 (0)	

NOTE. Statistically significant *P* values are shown in boldface.

The overall mortality rate for fungal infection among autologous HSCT recipients was 0.4% (95% CI, 0.2%–0.8%), with an IFI AMR of 34.8% (95% CI, 17.6%–55.5%; 8 deaths among 23 patients with proven or probable fungal infection). The overall rate of mortality due to *Candida* infection was 0.4% (95% CI, 0.2%–0.7%; 7 deaths among 1979 autologous HSCT recipients), with a *Candida* infection AMR of 43.8% (95% CI, 21.5%–68.0%; 7 deaths among 16 patients with *Candida* infection). Outcome was poorer among patients with infections due to non-*albicans Candida* strains than among those with *C. albicans* infection, although the difference was not significant (50% vs. 33%; $P = .5$).

Only 1 patient (<0.1%; 95% CI, 0.02%–0.2%) died of aspergillosis; the aspergillosis AMR was 14.3% (95% CI, 0.7%–53.0%; 1 death among 7 patients with proven or probable *Aspergillus* infection). Univariate and multivariate analysis did not identify any significant variable influencing outcome.

Comparison between the 2 HSCT procedures. The overall incidence of IFI was significantly higher among allogeneic HSCT recipients than among autologous HSCT recipients (7.8% vs. 1.2%; RR, 6.75; 95% CI, 4.31–10.57; $P < .001$). Aspergillosis was significantly more common after allogeneic HSCT than after autologous HSCT (6.3% vs. 0.3%; RR, 17.88; 95% CI, 8.28–38.61; $P < .001$). No difference emerged for *Candida* infection (1.2% vs. 0.8%; RR, 1.39; 95% CI, 0.68–2.83; $P = .3$).

The overall mortality rate was significantly higher after allogeneic HSCT (5.7%) than after autologous HSCT (0.4%; RR, 14.06; 95% CI, 6.7–29.11; $P < .001$). The aspergillosis AMR was significantly greater after allogeneic HSCT (77%) than after autologous HSCT (14%; RR, 3.49; 95% CI, 0.55–22.02; $P = .08$). No intergroup difference emerged with regard to the *Candida* infection AMR (57% vs. 44%; RR, 1.19; 95% CI, 0.52–2.74; $P = .67$).

It is worth noticing that all IFIs appeared soon after transplantation in autologous HSCT recipients, whereas patients receiving allogeneic HSCT continued to be at risk even after 100 days (table 7).

DISCUSSION

Our data confirm that aspergillosis is the major invasive fungal complication in allogeneic HSCT recipients but not in autologous HSCT recipients [9–12]. *A. fumigatus* was the most frequently isolated species. This finding does not concur with recent reports showing that molds other than *Aspergillus* species have been increasing in frequency over the past decade [23, 33]. In our population, infections due to other molds were extremely rare, with a ratio of infection due to *Aspergillus* species to that due to other molds of approximately 15:1. The rarity precludes any conclusion on the mortality rate of these other molds.

Among the HSCT recipients in our study, the incidence of IFI increased in 2002 and 2003, whereas the IFI AMR seems to have decreased. In our view, this was associated with the use of a better and more timely means of diagnostic evaluation, particularly for mold infections. More frequent use of high-resolution CT and better correlation of clinical pictures with serologic test results [34] probably led to detection of more infections and to use of more-appropriate therapeutic approaches. Furthermore, changes in transplantation practices, such as the use of alemtuzumab for GVHD prophylaxis or the use of reduced-intensity conditioning, which is usually associated with a higher incidence of chronic GVHD, may also have facilitated IFI, because these measures had already been implemented (although they had not been implemented at every center at the time of our study).

The incidence of mold infection was low among patients who underwent a total body irradiation–based conditioning regimen, possibly because total body irradiation favors engraftment and neutrophil recovery and reduces posttransplantation relapse [11].

The onset of IFI occurred at different times for each transplantation procedure. In autologous HSCT recipients, neutropenia was the major risk factor, whereas in allogeneic HSCT, IFI also developed in the late posttransplantation period because of persistent immune deficiency, which was mainly secondary to GVHD and its therapy. Such differences were particularly evident with regard to yeast infections.

A meta-analysis of 50 studies of aspergillosis revealed mortality rates of up to 90% among allogeneic HSCT recipients [20]. Overall, in our study of autologous and allogeneic HSCT, the aspergillosis AMR was ~70%, but it was dramatically higher for allogeneic HSCT recipients (77% vs. 14%). The influence of systemic antifungal prophylaxis with fluconazole on outcome for patients who developed invasive aspergillosis was suspected at univariate analysis, but it was not confirmed by multivariate analysis. The role of this prophylaxis is still debated: it probably

protects patients against yeasts but could favor the onset of very aggressive *Aspergillus* infections [25]. A more recent study hypothesizes that pretransplantation exposure to fluconazole inhibits subsequent killing activity of amphotericin B [35]. Upton et al. [36] reported that the outcome of aspergillosis recently improved as a result of advances in clinical practice, such as more prompt diagnosis, use of peripheral blood stem cells in transplants, and widespread use of voriconazole. None of these variables influenced the outcome in our analysis of aspergillosis. Conflicting results probably reflect the difficulty of obtaining clear conclusions from retrospective studies and the presence of many host variables and comorbidities (e.g., disease stage at transplantation, GVHD, and CMV infection) that could account for differences in the results of observational studies.

Candida species were the only yeast pathogens that we observed. Interestingly, the incidence of candidemia was similar among allogeneic and autologous HSCT recipients, suggesting that the type of transplantation was not a risk factor. Although the incidence was low, the *Candida*-related mortality rates among allogeneic HSCT and autologous HSCT recipients were higher than those noted in other reports [6–8]; this is possibly associated with the systematic administration of prophylaxis with fluconazole at almost all of the centers, resulting in induced selection of drug-resistant *Candida* strains. In fact, Marr et al. [6] reported that the primary cause of death associated with candidemia was non-*albicans* strains of *Candida,* which are generally more aggressive and difficult to treat. The influence of previous antifungal prophylaxis with fluconazole on the distribution of different *Candida* species has already been ascertained elsewhere [37, 38]. Furthermore, it recently has been reported that fluconazole may also induce resistance among *C. albicans* strains [39]. However, among the patients who underwent allogeneic HSCT in our study, the ratio of *C. albicans* to non-*albicans Candida* species was 1:1, and the *Candida* infection AMR was equally distributed in both groups; consequently, the use of fluconazole cannot be the only explanation for such trends. It is possible that the delayed identification of yeasts on blood culture could have played a role.

Despite the limits of our statistical analysis associated with the few cases that we analyzed, our data confirm that patients who undergo allogeneic HSCT have a high risk of developing IFI and that the IFI AMR remains very high. This information may help hematologists plan means of preventing aspergillosis in allogeneic HSCT recipients by using new, wide-spectrum antifungal agents and improve the management of fungal complications [40–42].

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