

Factors Associated with Mortality in Transplant Patients with Invasive Aspergillosis

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Background. Invasive aspergillosis (IA) is an important cause of morbidity and mortality in hematopoietic stem cell transplant (HSCT) and solid organ transplant (SOT) recipients. The purpose of this study was to evaluate factors associated with mortality in transplant patients with IA.

Methods. Transplant patients from 23 US centers were enrolled from March 2001 to October 2005 as part of the Transplant Associated Infection Surveillance Network. IA cases were identified prospectively in this cohort through March 2006, and data were collected. Factors associated with 12-week all-cause mortality were determined by logistic regression analysis and Cox proportional hazards regression.

Results. Six-hundred forty-two cases of proven or probable IA were evaluated, of which 317 (49.4%) died by the study endpoint. All-cause mortality was greater in HSCT patients (239 [57.5%] of 415) than in SOT patients (78 [34.4%] of 227; $P < .001$). Independent poor prognostic factors in HSCT patients were neutropenia, renal insufficiency, hepatic insufficiency, early-onset IA, proven IA, and methylprednisolone use. In contrast, white race was associated with decreased risk of death. Among SOT patients, hepatic insufficiency, malnutrition, and central nervous system disease were poor prognostic indicators, whereas prednisone use was associated with decreased risk of death. Among HSCT or SOT patients who received antifungal therapy, use of an amphotericin B preparation as part of initial therapy was associated with increased risk of death.

Conclusions. There are multiple variables associated with survival in transplant patients with IA. Understanding these prognostic factors may assist in the development of treatment algorithms and clinical trials.

Invasive aspergillosis (IA) is an important cause of morbidity and mortality in hematopoietic stem cell transplant (HSCT) and solid organ transplant (SOT) recipients. Despite improvements in the antifungal armamentarium and diagnostic modalities, mortality remains un-

acceptably high [1, 2]. Because of the poor outcomes associated with IA in transplant patients, there is much interest in prevention and treatment measures. Identification of prognostic factors may help to determine which patients require risk modification and/or more aggressive treatment.

Risk factors for IA have been studied extensively in transplant patients, but there are few studies that specifically describe variables related to outcomes [3–7]. These studies are difficult to perform for several reasons. First, studies are limited by the small numbers of patients and the low prevalence of IA at individual institutions. Second, defining outcome endpoints (all-cause vs attributable mortality) and the appropriate timing of endpoint determination is controversial. Finally, to predict which variables may contribute to outcomes,

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given the myriad factors that likely influence response to therapy and mortality (ie, predicting the most important variables), is challenging. Several studies document the importance of underlying immunosuppression, comorbid conditions, and disseminated infection as factors impacting survival [3–6]. Herein we analyzed the Transplant Associated Infection Surveillance Network (TRANSNET) database to determine factors associated with mortality among patients with IA.

METHODS

TRANSNET is a Centers for Diseases Control and Prevention– and industry-cosponsored prospective surveillance network composed of 23 US transplant centers, with the University of Alabama at Birmingham serving as the coordinating center [8]. Enrollment in the cohort of transplant recipients occurred during the period from March 2001 through September 2005. The period of surveillance for proven and probable invasive mycoses was from March 2001 through March 2006. Patients with proven or probable IA based on modified European Organization for Research and Treatment of Cancer/Mycoses Study Group criteria were included [9]. Modifications included applying the Ascioglu criteria to SOT patients and allowing bronchoalveolar lavage galactomannan as a diagnostic modality. There was no specified cytomegalovirus (CMV) prophylaxis, fungal prophylaxis, or immunosuppressive regimen as part of the study. From 31,823 screened transplant patients, a total of 2199 mycoses were identified, including 652 IA cases. This study includes 642 IA cases for which 12-week outcome data were available.

Clinical data and definitions. Patient data included demographics, transplant type, underlying diseases, site(s) of IA, and *Aspergillus* species. Data were also collected on other potential risk factors, including neutropenia, graft rejection or graft-versus-host disease (GVHD), CMV disease, antifungal prophylaxis and treatment, and other comorbidities. Early-onset IA was defined as a diagnosis <30 days after transplantation. Neutropenia was defined as an absolute neutrophil count <500 cells/mm³ within 30 days prior to diagnosis of IA, representing pre- or postengraftment neutropenia. CMV disease was defined as CMV detected in blood (by use of antigen or polymerase chain reaction assays), or histopathologic evidence of CMV, in association with signs and symptoms consistent with infection [4, 5]. GVHD was defined as greater than grade II GVHD. The following definitions of comorbid conditions were applied at the time of diagnosis of IA: renal insufficiency as a creatinine level ≥ 3.0 mg/dL or a creatinine clearance <30 mL/min [4]; corticosteroid use as any systemic use; hepatic insufficiency as ascites, other clinical stigmata of liver disease, or abnormal laboratory values (prothrombin time, international normalized ratio, and liver enzyme tests); malnutrition as a serum albumin level <2 g/dL or $\leq 5\%$ ideal body weight if albumin level is

2.1–2.5 g/dL. Disseminated IA was defined as extrapulmonary disease, excluding sinus disease. Mould-active antifungal prophylaxis was defined as receipt of any systemic mould-active antifungal agent in the 3 months prior to diagnosis of IA, excluding use for empiric or preemptive therapy. Antifungal treatment data included the specific agent and first date of administration. For the purposes of this study, primary combination therapy was defined as the administration of 2 anti-*Aspergillus* antifungals within 48 hours as initial therapy. The primary outcome endpoint was all-cause mortality 12 weeks after diagnosis of IA.

Statistical analysis. For analysis of the relationships of variables to survivors and nonsurvivors, univariate analyses were performed using the 2-group χ^2 test or the Fisher exact test for categorical variables and the 2-group *t* test for continuous variables. Multivariable analyses of factors associated with mortality were performed using stepwise multiple logistic regression analysis. Models using mortality as the dependent variable were determined separately for HSCT and SOT patients. All variables significant at $\alpha = .20$ in univariate analyses were considered as possible predictor variables for multivariable analyses. The criterion for entry into the model was significance at $\alpha = .20$, whereas the criterion for remaining in the model was significance at $\alpha = .05$. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated. Model fit was assessed using the Hosmer-Lemeshow goodness-of-fit statistic, and all models fit the data well. A multiple logistic regression model containing the best predictor variables obtained from the stepwise analysis was then run using all available data in order to obtain more robust estimates of the ORs, 95% CIs, and *P* values. For HSCT patients, a potential interaction between methylprednisone use and GVHD was evaluated by incorporating an interaction term into the final model obtained through multiple logistic regression analysis. For SOT patients, a potential interaction between prednisone use and rejection was evaluated by incorporating an interaction term into the final model obtained through multiple logistic regression analysis.

A time-to-death analysis was performed. Univariate analyses for SOT or HSCT patients were performed using the Kaplan-Meier method and the log-rank test. Multivariable analyses for factors associated with time to death were performed using stepwise Cox regression analysis, separately for HSCT and SOT patients. All variables significant at $\alpha = .20$ in univariate analyses were considered as possible predictor variables for the multivariable analyses. The criterion for entry into the model was significance at $\alpha = .20$; the criterion for remaining in the model was significance at $\alpha = .05$. Hazard ratios and their corresponding 95% CIs were calculated. A multivariable Cox proportional hazards model containing the best predictor variables obtained from the stepwise analysis was then run using all available data in order to obtain more robust estimates of the hazard ratios,

95% CIs, and *P* values. For HSCT patients, a potential interaction between methylprednisone use and GVHD was evaluated by incorporating an interaction term into the final model obtained through multivariable Cox regression analysis. For SOT patients, a potential interaction between prednisone use and rejection was evaluated by incorporating an interaction term into the final model obtained through multivariable Cox regression analysis. All statistical tests were 2-tailed and were performed using a 5% significance level ($\alpha = .05$). Statistical analyses were performed using SAS, version 9.1.3 (SAS Institute).

RESULTS

Clinical characteristics. Of 652 IA patients enrolled in TRANSNET during the study period, 642 were evaluated to determine factors associated with mortality (Tables 1 and 2). The 12-month cumulative incidence of IA was 1.6% in HSCT patients and 0.63% in SOT patients. The mean age was 49 years; 61% were male, 84% were white, and 64.6% were HSCT recipients. Twelve-week all-cause mortality was 49.4% and was greater among HSCT recipients than among SOT recipients (57.5% vs 34.4%; $P < .001$) (Figures 1 and 2). *Aspergillus fumigatus* was the most common species isolated (49.8%), whereas *A. niger* (7.6%), *A. flavus* (7.2%), and *A. terreus* (4.8%) were less common.

Factors associated with mortality in HSCT patients. Characteristics among the HSCT recipients, including neutropenia (54%), fever (49.9%), and greater than grade II GVHD (40%) are depicted in Table 1. By univariate analysis, it was found that nonsurvivors were more likely than survivors to have the following characteristics: allogeneic SCT (86.1% vs 74.4%; $P = .002$), neutropenia (59% vs 47.1%; $P = .017$), CMV disease (29.3% vs 19.3%; $P = .02$), renal insufficiency (36.4% vs 17.6%; $P < .001$), hepatic insufficiency (31.4% vs 6.3%; $P < .001$), malnutrition (20.9% vs 10.8%; $P = .006$), proven IA (34.7% vs 17.1%; $P < .001$), methylprednisolone use (39.3% vs 21%; $P < .001$), central nervous system (CNS) IA (8.8% vs 2.3%; $P = .006$), and disseminated IA (20.9% vs 9.1%; $P = .001$).

Multivariable logistic regression analysis demonstrated that neutropenia (OR, 2.3; 95% CI, 1.4–4.1), renal insufficiency (OR, 2.2; 95% CI, 1.2–3.8), hepatic insufficiency (OR, 6.2; 95% CI, 2.8–13.5), early-onset (<30 days) IA (OR, 2.2; 95% CI, 1.2–3.8), proven IA (OR, 2.4; 95% CI, 1.4–4.1), and methylprednisolone use (OR, 1.9; 95% CI, 1.1–3.2) were independently associated with mortality. White race was associated with decreased mortality risk (OR, 0.4; 95% CI, 0.2–0.8) (Table 3). After incorporation of an interaction term of GVHD and methylprednisone use into the final model, there was evidence of an interaction between GVHD and methylprednisone ($P = .025$). A time-to-death analysis was performed for confirmation of findings. Cox regression modeling showed similar findings to the logistic regression model, with the exception of neutro-

penia and early-onset IA, which were not poor prognostic indicators (data not shown).

Factors associated with mortality in SOT patients. Among SOT recipients, the lung was the most frequently transplanted organ (47.1%), followed by the kidney (20.7%), the liver (18.5%), and the heart (10.1%). Characteristics among the SOT recipients are shown in Table 2, including prednisone use (76.7%), renal insufficiency (46.7%), organ rejection (49.3%), and CMV disease (22.5%). By univariate analysis, it was found that nonsurvivors were more likely than survivors to have the following characteristics: kidney (29.5% vs 16.1%; $P = .018$) or liver (32.1% vs 11.4%; $P < .001$) transplantation, renal insufficiency (62.8% vs 38.3%; $P < .001$), hepatic insufficiency (8.2% vs 5.4%; $P < .001$), malnutrition (35.9% vs 14.1%; $P < .001$), proven IA (55.1% vs 35.6%; $P = .005$), use of methylprednisolone (29.5% vs 13.4%; $P = .003$), CNS IA (16.7% vs 2%; $P < .001$), and disseminated IA (32.1% vs 16.1%; $P = .006$). Lung transplantation (29.5% vs 56.4%; $P < .001$) and prednisone use (62.8% vs 83.9%; $P < .001$) were less frequent among nonsurvivors than among survivors.

Multivariable logistic regression analysis demonstrated that hepatic insufficiency (OR, 3.9; 95% CI, 1.3–11.8), malnutrition (OR, 2.3; 95% CI, 1.0–5.1), and CNS disease (OR, 6.6; 95% CI, 1.4–29.9) were independently associated with increased risk of death. Prednisone use (OR, 0.4; 95% CI, 0.2–0.8) was associated with decreased risk of death (Table 3). After the incorporation of an interaction term of rejection and prednisone in the final model, no statistically significant interaction was observed. Multivariable Cox regression demonstrated findings similar to the logistic regression model. Important exceptions were that kidney transplantation (OR, 1.7; 95% CI, 1.0–3.0) and white race (OR, 0.5; 95% CI, 0.2–1.0) were predictors of mortality. Malnutrition was not a poor prognostic indicator.

Antifungal therapy and impact on mortality. A subanalysis of the impact of antifungal therapy on mortality was performed for 550 patients who received antifungal therapy (Tables 1, 2, and 4). Among 348 HSCT patients, receipt of an amphotericin B (AmB) formulation as part of initial antifungal therapy was more common among nonsurvivors than among survivors (47.7% vs 33.1%; $P = .006$); receipt of voriconazole was less common among nonsurvivors than among survivors (39.1% vs 53.6%; $P = .007$). There was no significant association of primary combination antifungal therapy with death. Multivariable logistic regression analysis demonstrated that receipt of an AmB formulation as initial therapy was associated with increased mortality (OR, 2.2; 95% CI, 1.3–3.7) (Table 4). A Cox proportional hazards model (data not shown) provided similar results.

Among 202 SOT patients, receipt of an AmB formulation as part of initial antifungal therapy was more common among nonsurvivors than among survivors (60.6% vs 29.8%; $P <$

Table 1. Characteristics of 415 Hematopoietic Stem Cell Transplant Patients with Invasive Aspergillosis (IA)

Characteristic	Total (n = 415)	Survivors ^a (n = 176)	Nonsurvivors (n = 239)	P ^b
Age, mean ± SD, years	46.9 ± 15.6	47.3 ± 16.9	46.6 ± 14.6	.68
Male sex	260/414 (62.8)	108/176 (61.4)	152/238 (63.9)	.60
White race	343/384 (89.3)	151/163 (92.6)	192/221 (86.9)	.07
Hematopoietic stem cell transplant				
Allogeneic	337/415 (81.2)	131/176 (74.4)	206/239 (86.1)	.002
Matched related ^c	168/337 (49.9)	71/131 (54.2)	97/206 (47.1)	.20
Autologous	78/415 (18.8)	45/176 (25.6)	33/239 (13.8)	
Myeloablative conditioning	288/415 (69.4)	117/176 (66.5)	171/239 (71.6)	.27
Neutropenia ^d	224/415 (54.0)	83/176 (47.1)	141/239 (59.0)	.017
Fever ^e	207/415 (49.9)	84/176 (47.7)	123/239 (51.5)	.45
Graft-versus-host disease ^f	135/337 (40)	48/131 (39)	87/206 (61.1)	.30
Cytomegalovirus disease ^g	104/415 (25.1)	34/176 (19.3)	70/239 (29.3)	.021
Renal insufficiency ^h	118/415 (28.4)	31/176 (17.6)	87/239 (36.4)	<.001
Hepatic insufficiency ⁱ	86/415 (20.8)	11/176 (6.3)	75/239 (31.4)	<.001
Malnutrition ^j	69/415 (16.6)	19/176 (10.8)	50/239 (20.9)	.006
Diabetes	116/415 (28.0)	43/176 (24.4)	73/239 (30.5)	.17
Early-onset IA ^k	147/401 (36.7)	70/174 (40.2)	77/227 (33.9)	.19
Proven IA (vs probable IA)	113/415 (27.2)	30/176 (17.1)	83/239 (34.7)	<.001
<i>Aspergillus fumigatus</i>	183/415 (44.1)	69/176 (39.2)	114/239 (47.7)	.085
Prednisone use ^l	134/415 (32.3)	64/176 (36.4)	70/239 (29.3)	.13
Methylprednisone use ^l	131/415 (31.6)	37/176 (21.0)	94/239 (39.3)	<.001
Site of IA				
Pulmonary	385/415 (92.8)	166/176 (94.3)	219/239 (91.6)	.29
Central nervous system	25/415 (6.0)	4/176 (2.3)	21/239 (8.8)	.006
Disseminated ^m	66/415 (15.9)	16/176 (9.1)	50/239 (20.9)	.001
Mould-active prophylaxis	115/415 (27.7)	47/176 (26.7)	68/239 (28.5)	.69
Antifungal therapy ⁿ				
Combination therapy ^o	100/348 (28.7)	41/151 (27.1)	59/197 (29.9)	.57
Voriconazole	158/348 (45.4)	81/151 (53.6)	77/197 (39.1)	.007
Caspofungin	143/348 (41.1)	58/151 (38.4)	85/197 (43.2)	.37
Amphotericin B formulation	144/348 (41.4)	50/151 (33.1)	94/197 (47.7)	.006
Lipid amphotericin B	134/348 (38.5)	49/151 (32.5)	85/197 (43.2)	.042
Amphotericin B	10/348 (2.9)	1/151 (0.7)	9/197 (4.6)	.048
Itraconazole	10/348 (2.9)	5/151 (3.3)	5/197 (2.5)	.75

NOTE. Data are proportion (%) of patients, unless otherwise indicated. SD, standard deviation.

^a Mortality defined at 12 weeks after IA diagnosis.

^b Determined by use of the χ^2 test or the Fisher exact test for categorical variables and the *t* test for the variable of age.

^c When compared with other (matched unrelated, mismatched related, and cord blood).

^d Defined as absolute neutrophil count <500 cells/mm³ within 30 days prior to IA diagnosis.

^e Temperature >100.5°C after 7 days of IA diagnosis.

^f Defined as >grade II graft-versus-host disease.

^g Positive antigen, culture, or histopathology in association with signs and symptoms consistent with cytomegalovirus disease.

^h Defined as serum creatinine level >3.0 mg/dL or creatine clearance <30 mL/min at diagnosis of IA.

ⁱ Hepatic insufficiency was defined as ascites, stigmata of liver disease, or elevated laboratory values related to the liver (prothrombin time, international normalized ratio, and liver function tests) at time of diagnosis of IA.

^j Serum albumin level <2 g/dL or ≤5% ideal body weight if albumin level is 2.1–2.5 g/dL.

^k IA diagnosis <30 days after transplant.

^l Use at time of diagnosis of IA.

^m Defined as extrapulmonary disease, excluding sinuses.

ⁿ Data available for 348 patients and refer to drug(s) used in initial regimen (primary therapy).

^o Combination therapy defined as initiation of 2 antifungal agents within 48 hours as primary therapy.

Table 2. Characteristics of 227 Solid Organ Transplant Patients with Invasive Aspergillosis (IA)

Characteristic	Total (n = 227)	Survivors ^a (n = 149)	Nonsurvivors (n = 78)	P ^b
Age, mean ± SD, years	52.9 ± 13.3	52.6 ± 12.8	53.4 ± 14.3	.67
Male sex	130/224 (58.0)	79/146 (54.2)	51/78 (65.4)	.10
White race	197/220 (89.6)	129/142 (90.9)	68/78 (87.2)	.40
Solid organ transplant ^c				
Lung	107/227 (47.1)	84/149 (56.4)	23/78 (29.5)	<.001
Kidney	47/227 (20.7)	24/149 (16.1)	23/78 (29.5)	.018
Liver	42/227 (18.5)	17/149 (11.4)	25/78 (32.1)	<.001
Heart	23/227 (10.1)	18/149 (12.1)	5/78 (6.4)	.18
Other ^d	8/227 (3.5)	6/149 (4.0)	2/78 (2.6)	.72
Fever ^e	87/227 (38.3)	52/149 (34.9)	35/78 (44.9)	.14
Organ rejection ^f	112/227 (49.3)	71/149 (47.7)	41/78 (52.6)	.48
Cytomegalovirus disease ^g	51/227 (22.5)	30/149 (20.3)	21/78 (26.9)	.24
Renal insufficiency ^h	106/227 (46.7)	57/149 (38.3)	49/78 (62.8)	<.001
Liver insufficiency ⁱ	30/227 (13.2)	8/149 (5.4)	22/78 (28.2)	<.001
Malnutrition ^j	49/227 (21.6)	21/149 (14.1)	28/78 (35.9)	<.001
Diabetes	105/227 (46.3)	66/149 (44.3)	39/78 (50.0)	.41
<i>Aspergillus fumigatus</i>	137/227 (60.4)	84/149 (56.4)	53/78 (68.0)	.091
Proven IA (vs probable IA)	96/227 (42.3)	53/149 (35.6)	43/78 (55.1)	.005
Prednisone use ^k	174/227 (76.7)	125/149 (83.9)	49/78 (62.8)	<.001
Methylprednisone use ^k	43/227 (18.9)	20/149 (13.4)	23/78 (29.5)	.003
IA onset >30 days after transplant	164/226 (72.6)	108/149 (72.5)	56/77 (72.7)	.97
Site of IA				
Pulmonary	206/227 (90.8)	134/149 (89.9)	72/78 (92.3)	0.56
Disseminated ^l	49/227 (21.6)	24/149 (16.1)	25/78 (32.1)	.006
Central nervous system	16/227 (7.0)	3/149 (2.0)	13/78 (16.7)	<.001
Antifungal therapy ^m				
Combination therapy ⁿ	56/202 (27.7)	38/131 (29.0)	18/71 (25.4)	.58
Voriconazole	95/202 (47.0)	75/131 (57.3)	20/71 (28.2)	<.001
Caspofungin	53/202 (26.2)	29/131 (22.1)	24/71 (33.8)	.072
Amphotericin B formulation	82/202 (40.6)	39/131 (29.8)	43/71 (60.6)	<.001
Lipid amphotericin B	70/202 (34.7)	33/131 (25.2)	37/71 (52.1)	<.001
Amphotericin B	12/202 (5.9)	6/131 (4.6)	6/71 (8.5)	.35
Itraconazole	28/202 (13.9)	25/131 (19.1)	3/71 (4.2)	.004

NOTE. Data are proportion (%) of patients, unless otherwise indicated. SD, standard deviation.

^a Mortality defined at 12 weeks after IA diagnosis.

^b Determined by use of the χ^2 test or the Fisher exact test for categorical variables and the *t* for the variable of age.

^c *P* value represents analysis of organ type vs all others.

^d Pancreas, small bowel, or multiple organ transplants; defined as absolute neutrophil count <500 cells/mm³ within 30 days prior to IA diagnosis.

^e Temperature >100.5°C after 7 days of IA diagnosis.

^f Acute or chronic rejection at time of IA diagnosis.

^g Positive antigen, culture, or histopathology in association with signs and symptoms consistent with cytomegalovirus disease.

^h Defined as serum creatinine level >3.0 mg/dL or creatine clearance <30 mL/min at diagnosis of IA.

ⁱ Hepatic insufficiency was defined as ascites, stigmata of liver disease, or elevated laboratory values related to the liver (prothrombin time, international normalized ratio, and liver function tests) at time of diagnosis of IA.

^j Serum albumin level <2 g/dL or ≤5% ideal body weight if albumin level is 2.1–2.5 g/dL.

^k Use at time of diagnosis of IA.

^l Defined as extrapulmonary disease, excluding sinuses.

^m Data available for 202 patients and refer to drug(s) used in initial regimen (primary therapy).

ⁿ Combination therapy defined as initiation of 2 antifungal agents within 48 hours as primary therapy.

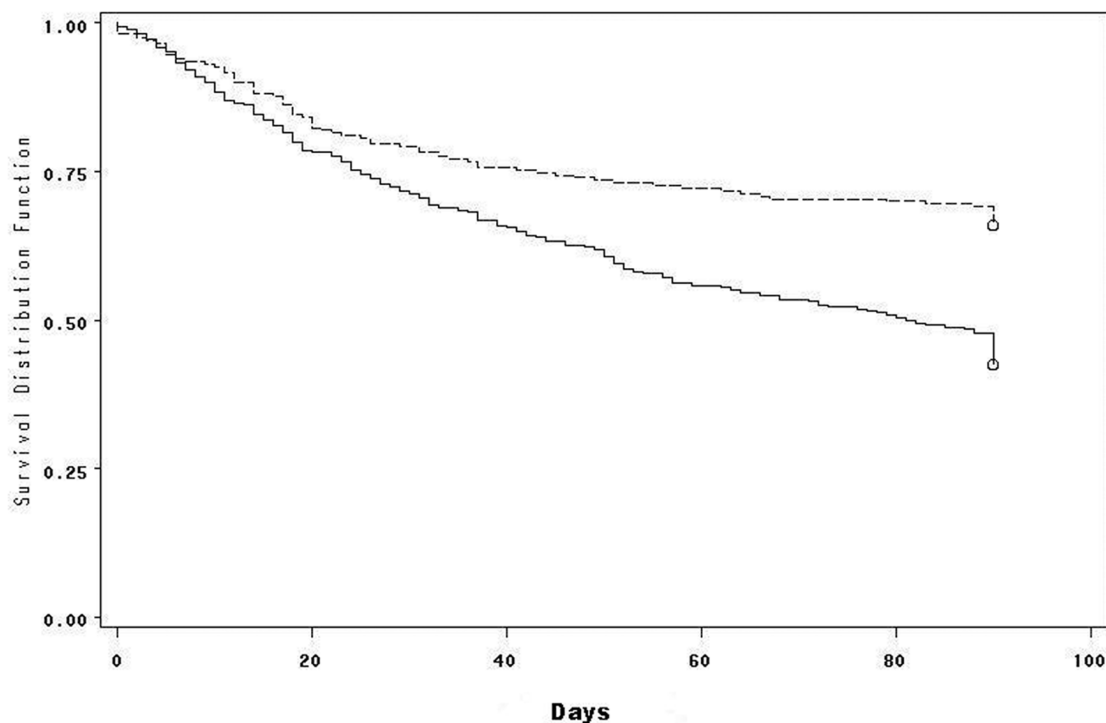


Figure 1. Kaplan-Meier probability of survival after diagnosis of invasive aspergillosis according to transplant type. Survival of solid organ transplant patients (*top curve, dashed line*) is compared with that of hematopoietic stem cell transplant patients (*bottom curve, solid line*; $P < .001$)

.001). In contrast, receipt of voriconazole (28.2.1% vs 57.3%; $P < .001$) or itraconazole (4.2% vs 19.1%; $P = .004$) was less common among nonsurvivors than among survivors. There was no significant association of primary combination anti-fungal therapy with death. Multivariable logistic regression

analysis showed that receipt of an AmB formulation (OR, 4.4; 95% CI, 2.1–9.1) or caspofungin (OR, 2.7; 95% CI, 1.1–6.3) was associated with increased mortality (Table 4). A Cox proportional hazards model (data not shown) confirmed these findings.

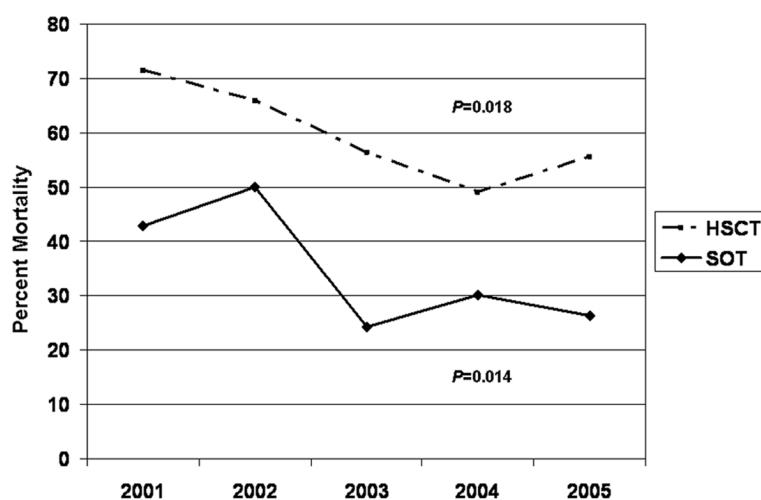


Figure 2. Mortality per year during the study. For both transplant groups (solid organ transplant [SOT] patients and hematopoietic stem cell transplant [HSCT] patients), there was a significant linear trend in decreased mortality (Cochran-Armitage trend test). Data for years 2005 and 2006 are combined, because only 13 patients developed invasive aspergillosis in 2006.

Table 3. Multivariable Logistic Regression Analysis of Factors Associated with Mortality among 415 Hematopoietic Stem Cell Transplant (HSCT) Patients with Invasive Aspergillosis (IA) and 227 Solid Organ Transplant (SOT) Patients with IA

Model, variable	OR (95% CI)	P ^a
HSCT-specific model		
Age	1.0 (0.99–1.02)	.57
Male sex	1.1 (0.6–1.7)	.82
White race	0.4 (0.2–0.8)	.017
Neutropenia	2.3 (1.4–4.1)	.002
Renal insufficiency	2.2 (1.2–3.8)	.007
Hepatic insufficiency	6.2 (2.8–13.5)	<.001
Early-onset IA	2.2 (1.2–3.8)	.007
Proven IA (vs probable IA)	2.4 (1.4–4.1)	.002
Methylprednisone use	1.9 (1.1–3.2)	.016
SOT-specific model		
Age	1.0 (0.99–1.05)	.11
Male sex	1.7 (0.9–3.3)	.13
White race	0.4 (0.1–1.2)	.11
Hepatic insufficiency	3.9 (1.3–11.8)	.015
Malnutrition	2.3 (1.0–5.1)	.044
Prednisone use	0.4 (0.2–0.8)	.011
CNS disease	6.6 (1.4–29.9)	.015

NOTE. CI, confidence interval; CNS, central nervous system; OR, odds ratio.

^a Variables with $P < .20$ on univariate analysis were included in stepwise regression models in addition to variables for age, race, and sex. Only statistically significant P values ($P < .05$) are shown.

DISCUSSION

There has been dramatic improvement in the early diagnosis and treatment of transplant-associated IA over the past decade [10–14]. Identification of important prognostic factors could influence patient outcomes through improved prevention and treatment strategies [1, 4]. To date, there have been several IA outcomes studies among HSCT recipients, but few studies among SOT recipients [6, 7, 15]. This analysis of the TRANSNET database, a large, prospectively collected cohort of HSCT and SOT recipients, for the first time identified important factors associated with mortality in both transplant populations. Using 2 different analytic methodologies to assess mortality risk provided similar, but not identical, results, highlighting the complexity in analyzing outcomes in these patients.

Overall mortality at 12 weeks among HSCT patients was 57.5%, consistent with the poor outcomes described in previous studies [3–5, 16–18]. Independent prognostic factors included neutropenia, renal insufficiency, hepatic insufficiency, early-onset IA, proven IA, and methylprednisolone use. Using a time-to-death analysis, we found that neutropenia and early-onset IA did not predict mortality. The majority of studies to date

have recognized neutropenia as an important influence on mortality, underscoring the importance of immune system recovery among HSCT patients with IA [3, 4]. That these data do not consistently demonstrate this association may be related to our definition of neutropenia. We did not collect detailed laboratory data as part of this study but rather reported any episode of neutropenia, defined as an absolute neutrophil count <500 cells/mm³, within 30 days prior to IA diagnosis.

Renal insufficiency and hepatic insufficiency were predictors of mortality among HSCT patients with IA; both have been associated with poor outcomes in previous studies [4–6]. In our population, hepatic insufficiency was the strongest predictor of mortality (OR, 6.2), confirming the findings of one study among HSCT patients with IA [4], possibly explained by the complexity of drug delivery in these patients.

As demonstrated in prior experimental and observational studies, proven IA (as opposed to probable disease) is a predictor of poor outcomes [4, 6–10]. This intuitive observation—probable IA cases represent less diagnostic certainty—also suggests that proven IA may represent more advanced disease, even though this association was not affected by adjusting for disseminated IA in our final model.

Numerous studies have documented the impact of steroids on outcome in HSCT patients with IA, with receipt of high-

Table 4. Multivariable Logistic Regression Analysis of Factors Associated with Mortality among 550 Transplant Patients with Invasive Aspergillosis (IA) Who Received Antifungal Therapy

Model, variable	OR (95% CI)	P ^a
HSCT-specific model (348 patients)		
Age	1.0 (0.99–1.004)	.56
Male sex	1.0 (0.6–1.7)	.99
White race	0.3 (0.1–0.8)	.020
Allogeneic HSCT (vs autologous HSCT)	2.5 (1.2–5.0)	.010
Renal insufficiency	2.9 (1.6–5.4)	<.001
Hepatic insufficiency	5.6 (2.5–12.9)	<.001
Proven IA	1.9 (1.0–3.4)	.035
Amphotericin B formulation	2.0 (1.2–3.4)	.007
SOT-specific model (202 patients)		
Age	1.0 (0.99–1.05)	.20
Male sex	2.0 (0.9–4.4)	.076
White race	0.6 (0.2–1.8)	.34
Renal insufficiency	2.0 (1.0–4.1)	.047
Prednisone use	0.3 (0.1–0.7)	.005
CNS disease	5.4 (1.2–24.1)	.028
Amphotericin B formulation	4.4 (2.1–9.1)	<.001
Caspofungin	2.7 (1.1–6.3)	.023

NOTE. CI, confidence interval; CNS, central nervous system; HSCT, hematopoietic stem cell transplant; OR, odds ratio; SOT, solid organ transplant.

^a Variables with $P < .20$ on univariate analysis were included in stepwise regression models in addition to variables for age, race, and sex. Only statistically significant P values ($P < .05$) are shown.

dose (≥ 2 mg/kg) corticosteroids daily at the time of diagnosis being a precise predictor [2–6, 19]. We did not routinely collect data on daily corticosteroid doses and could not explore fully the impact of dose or duration on mortality, but among patients this reflects treatment for GVHD. GVHD did not fulfill criteria for stepwise entry into the final model, but we observed a significant interaction between GVHD and methylprednisolone.

We observed that white patients with IA had lower overall mortality, compared with other races. A clear racial predisposition to severe fungal disease has been best described among patients with coccidioidomycosis [20]. This is a novel observation among patients with IA, and explanations for this apparent predisposition may relate to less optimal donor matching or other confounding factors.

All-cause mortality at 12 weeks was 34.4% among SOT patients with IA and was lowest among lung transplant recipients. Independent predictors of mortality included hepatic insufficiency, malnutrition, and CNS disease. Prednisone use was associated with decreased risk of mortality, possibly representing more stable maintenance immunosuppression. Cox regression analysis and the logistic regression model revealed similar results, except that kidney transplantation and nonwhite race were poor prognostic indicators.

Several prior studies have linked CNS involvement with poor outcome [1, 5]. Although only 16 (7%) of 227 SOT patients had CNS IA, 13 (81%) of these patients died. Disseminated IA, defined as any extrapulmonary disease, was also a significant predictor of death in univariate analysis, similar to what has been reported elsewhere [1, 3, 4, 6]. Timeliness in diagnosis of IA among SOT patients remains an important issue, possibly contributing to the frequency of complicated IA in these patients. Except for routine posttransplant surveillance bronchoscopy in lung recipients, screening methods for IA are not regularly performed in SOT populations.

Antifungal management of IA remains problematic. Despite the availability of newer antifungal drugs, clinical response remains poor, and few randomized, comparative treatment trials are available [10, 21–23]. Combination antifungal therapy is attractive, but there are few prospective data to support this approach [7, 24–26]. Current guidelines endorse voriconazole monotherapy as the first-line choice for primary IA [10, 11]. In this study, voriconazole alone was the most common approach to primary therapy, whereas primary combination therapy was used in 28% of patients. We did not demonstrate that combination therapy had an impact on survival. In comparing those who did receive combination therapy with those who did not, we found that the underlying characteristics were similar with few exceptions. For example, HSCT patients who received combination therapy were more likely to be malnourished ($P = .001$) and older ($P = .01$) than those who did not. These findings alone likely do not explain the lack of an observed

difference among the groups; there may be confounding and unmeasured variables that more likely explain this observation.

We observed distinct differences in mortality according to the antifungal agents used. Use of an AmB formulation in HSCT or SOT patients resulted in increased risk of death at 12 weeks, despite adjustment for renal insufficiency. This confirms data from a recent trial associating initial AmB use with increased mortality [10]. Importantly, we observed decreasing mortality during our study period and a significant decrease in use of AmB over time. This observation has been described in several recent studies and may be related to differences in patient selection, supportive care, and/or newer antifungal agents [1, 27]. Survivors were more likely than nonsurvivors to have received voriconazole, and it was used with increasing frequency throughout the study, but it was not an independent predictor of mortality.

SOT patients who received caspofungin as initial therapy had an increased risk of death. Among these patients, there was an increased frequency of malnutrition ($P = .05$), liver disease ($P = .008$), renal insufficiency ($P = .06$), and CNS disease ($P = .09$), which suggests that SOT patients who received caspofungin were perceived to be more ill. Notably, caspofungin was commonly used as a combination agent with voriconazole or an AmB formulation.

Our study has several limitations, including lack of extensive laboratory data [4, 6]. Only data on antifungal drug type and start date were collected, thus insights into dose, duration, and combination therapy were limited. We did not analyze attributable mortality, because a standardized definition was not employed for TRANSNET. It is notable that, among 4 recent studies investigating predictors of IA attributable mortality, 3 different definitions of attributable mortality were used [3, 4, 6, 17]. This underscores the difficulty of defining mortality attributable to IA and the necessity of a consensus definition [21]. Our outcome analysis endpoint was 12 weeks after IA diagnosis. Recent reports suggest that early mortality is mostly attributable to IA, whereas later mortality is more likely related to other causes [28]. Our database lacked some variables that may impact overall survival, including risk of underlying disease, relapsed malignancy, and transplant incompatibility. Finally, we did not collect data on dose and duration of corticosteroid or other immunosuppressive use. Despite these limitations, this large and broadly based surveillance study provides greater credence to previous observations, and we are encouraged by the general concordance between prognostic factors described herein and those from previous studies.

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