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# Risk factors for recurrence of invasive fungal infection during secondary antifungal prophylaxis in allogeneic hematopoietic stem cell transplant recipients

F. Liu, T. Wu, J.B. Wang, X.Y. Cao, Y.M. Yin, Y.L. Zhao, D.P. Lu. Risk factors for recurrence of invasive fungal infection during secondary antifungal prophylaxis in allogeneic hematopoietic stem cell transplant recipients.
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**Abstract:** *Background.* Invasive fungal infections (IFIs) are a major cause of mortality among allogeneic hematopoietic stem cell transplantation (allo-HSCT) patients. Thanks to the widespread use of secondary antifungal prophylaxis (SAP), a history of IFI is not an absolute contraindication to allo-HSCT. However, IFI recurrence remains a risk factor for transplant-related mortality.
*Methods.* To evaluate the risk factors for IFI recurrence in allo-HSCT patients receiving SAP, we performed a retrospective analysis of 90 individuals treated at our hospital. SAP antifungal agents included fluconazole ($n$ = 28), voriconazole ($n$ = 25), itraconazole ($n$ = 23), caspofungin ($n$ = 7), and micafungin ($n$ = 7).
*Results.* By day +100, recurrent IFI had occurred in 23 (25.5%) patients. Our multivariate analysis identified 4 factors significantly associated with a risk of IFI recurrence within 100 days of allo-HSCT: duration of neutropenia >18 days, presence of severe acute graft-versus-host disease (aGVHD), <70-day interval between previous infection and transplantation, and use of a narrow-spectrum SAP agent ($P$ = 0.008, 0.010, 0.041, and 0.001, respectively). Of the 87 patients who remained in the study for the duration of the follow-up period (median length: 551 days), 26 (29.9%) died; only 7 (8.0%) of these deaths resulted from a severe fungal infection.
*Conclusion.* These results suggest that transplantation outcome can be improved by adequate antifungal treatment before transplantation, better prevention of, and therapy for, severe aGVHD, use of granulocyte colony-stimulating factor to reduce the duration of neutropenia, and use of broad-spectrum prophylaxis agents.

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Invasive fungal infections (IFIs) are increasingly recognized as one of the leading causes of infection-induced mortality after allogeneic hematopoietic stem cell transplantation (allo-HSCT) (1, 2). Although major advances have recently been made in antifungal therapy, the risk of recurrent infections after HSCT is still high, and is associated with a poor outcome. Thus, to improve overall outcomes of HSCT, it is important to prevent IFIs (3–5).

Secondary antifungal prophylaxis (SAP) is prevention of recurrent IFI in patients who survived an IFI previously, and undergo an additional deeply immunosuppressive treatment phase including high-dose chemotherapy or HSCT. The aim of SAP is to prevent recurrence of a previous IFI or onset of another. Thanks to the widespread use of SAP—especially with mold-active antifungal agents—allo-HSCT is no longer

contraindicated for those with a history of IFI. Although use of SAP in allo-HSCT patients has received considerable attention, we are aware of no research investigating the risk factors for IFI recurrence under SAP in allo-HSCT recipients.

To address this gap in the literature, we retrospectively analyzed data of 90 patients who had a history of IFI undergoing allo-HSCT in our hospital. Specifically, we examined IFI recurrence and survival rates, as well as analyzing potential risk factors associated with early IFI recurrence.

## Patients and methods

### Study design and inclusion criteria

This study was a retrospective analysis of allo-HSCT patients treated in the HSCT department of the Beijing Dao-pei Hospital. Allo-HSCT patients were considered eligible for inclusion in the study if they had a history of possible, probable, or proven IFI that had been acquired during antecedent treatment, and if they had previously responded to antifungal treatment.

IFIs were defined according to the European Organization for Research and Treatment of Cancer/Mycoses Study Group guidelines (6). Briefly, a "positive diagnosis" required histopathologic or microbiologic documentation of a fungus from biopsied tissues, or positive results from culture of specimens obtained from a normally sterile site. A "probable infection" required host factors, clinical features including specific radiographic imaging signs and symptoms, and mycological evidence including an identified mold or a positive β-D-glucan (BG) test (Fungitec, Goldstream Co., Ltd., Tianjin, China; a level $\geq 20$ pg/mL was considered positive). Cases were considered "possible" when host factors and clinical evidence were consistent with IFI, but when mycological support could not be obtained. Patients were not included in the study if they had any contraindications against the antifungal drugs used for prophylaxis. As part of the consent procedure for HSCT, all patients provided written informed consent to be treated with SAP as a medically indicated measure of supportive care.

### Disease stage at transplant

Disease stage at transplant was categorized. For patients with acute myeloid leukemia, acute lymphoblastic leukemia, and non-Hodgkin's lymphoma, the early stage was defined as first complete remission, the intermediate stage as second complete remission or greater, and the advanced stage as refractory or relapse. For patients with chronic myeloid leukemia, the early stage was defined as the first chronic phase, the intermediate stage as the second chronic phase or greater or the accelerated phase, and the advanced stage as blast crisis. In patients with myelodysplastic syndrome, the early stage was defined as refractory anemia or refractory anemia with ringed sideroblasts, and the advanced stage as refractory anemia with excess blasts or refractory anemia with excess blasts in transformation.

### Antifungal prophylaxis

The antifungal prophylaxis agent used on the first day of conditioning differed among patients. Twenty-eight received the narrow-spectrum agent fluconazole, while the remaining patients ($n = 62$) received one of several possible broad-spectrum agents: voriconazole ($n = 25$), itraconazole ($n = 23$), caspofungin ($n = 7$), or micafungin ($n = 7$). The antifungal agent was chosen according to which category of infection patients had previously been diagnosed with, which treatment agents had previously been effective, financial capacity, and organ function. Most patients received the same agent with which they had previously been effectively treated. However, fluconazole was used for those with limited financial capacity and no definite evidence of mold infection. The less-toxic agents, caspofungin and micafungin, were prescribed for patients with organ dysfunction. For refractory cases, we used the highly efficient agent voriconazole.

Prophylaxis with broad-spectrum agents was continued until a median of 58 days (range: 14–120 days) after stem cell infusion, after which time patients were given fluconazole if they had no signs of active fungal infection. Prophylaxis was continued until the withdrawal of immunosuppressants. No therapeutic drug monitoring was performed for any agent.

### Patient monitoring and follow-up

During hospitalization, all the patients lived in single isolation rooms equipped with positive air pressure and high-efficiency air filters, and underwent daily clinical and biochemical assessment. Prophylactic trimethoprim-sulfamethoxazole and acyclovir were used to prevent *Pneumocystis jirovecii* and herpes simplex infections, as reported previously (7). Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine, mycophenolate mofetil, and short-term methotrexate. Most patients received granulocyte colony-stimulating

factor (5 μg/kg daily) from day 6 until neutrophil engraftment. Neutropenic fever episodes were treated with broad-spectrum antibiotics according to published guidelines. Additional cultures from blood, urine, and sputum, as well as from infected sites, were performed when clinically indicated. Diagnosis of IFI was performed, as clinically indicated, using high-resolution computed tomography and serum BG levels.

After patients were discharged from the hospital, we followed up with them at least once a week until day 120; depending on their clinical status, some patients received additional follow-ups thereafter. The final evaluation for all surviving patients was 30 January 2010. Clinical symptoms, computed tomography scans, and BG levels were used to assess response to fungal treatments.

### Analysis and statistics

We analyzed the proportion of patients with IFI recurrence by day 100 after stem cell infusion. Recurrence and survival rates were estimated using the Kaplan–Meier method and log-rank test. Risk factors for IFI recurrence were assessed using univariate ($\chi^2$ tests) and multivariate (logistic regressions) analyses.

The following variables were included in the univariate analyses: gender, age ($\leq 30$ or >30 years), type of graft (matched-related donor, matched-unrelated donor, mismatched-unrelated donor, or haploidentical-related donor), status of original disease (complete remission or not), human leukocyte antigen (HLA) disparity (matched or mismatched), continuous duration of neutropenia ($\leq 18$ or >18 days), presence or absence of grade III–IV acute GVHD (aGVHD), resolution of radiographic abnormalities during prior infection, reactivation of cytomegalovirus (CMV) infection, interval between the prior infection and transplantation (<70 or $\geq 70$ days), and type of prophylactic antifungal agent used (narrow- or broad-spectrum). Multivariate analyses were performed only on variables with $P < 0.25$ in univariate analyses. We calculated adjusted odds ratios and 95% confidence intervals. Significance was defined as $P < 0.05$. Analyses were performed with SPSS v.16 (SPSS Inc., Chicago, Illinois, USA).

## Results

### Demographics and baseline characteristics

Of the 690 patients who received allo-HSCT in our hospital between October 2004 and July 2009, 90 had a history of active IFI and could be included in this study.

The demographics and clinical characteristics of participants, including stem cell source and type of transplant, are shown in Table 1. The median age of patients was 26 years (range: 5–59). Sixty patients (67%) were male and 30 (33%) were female. The majority of grafts were haploidentical-related donor ($n = 46$), followed by matched-related donor ($n = 22$), then mismatched-unrelated donor ($n = 14$), and matched-unrelated donor ($n = 8$). The underlying diseases were mainly acute myeloid leukemia ($n = 39$) and acute lymphoblastic leukemia ($n = 37$), followed by chronic myeloid leukemia ($n = 6$), myelodysplastic syndrome ($n = 3$), and others ($n = 5$). In half (45 of 90) of all cases, the underlying hematologic disease was in an intermediate or advanced stage.

### Transplant characteristics, engraftment, and other transplant complications

All patients underwent myeloablative conditioning regimens following the protocols described in Lu et al.

**Demographic and medical characteristics of study subjects ($n = 90$)**

| Characteristic | *n* |
|---|---|
| Gender | |
| Male | 60 |
| Female | 30 |
| Age in years, median (range) | 26 (5–59) |
| Diagnosis | |
| AML | 39 |
| ALL | 37 |
| CML | 6 |
| MDS | 3 |
| NHL | 2 |
| Other | 3 |
| Transplant type | |
| Matched sibling donor | 22 |
| Unrelated donor | 22 |
| Haploidentical donor | 46 |
| Disease status | |
| Early stage | 45 |
| Intermediate stage | 22 |
| Advanced stage | 23 |

AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myeloid leukemia; MDS, myelodysplastic syndrome; NHL, non-Hodgkin's lymphoma.

*Table 1*

(7) and received allo-HSCT on day 0. All patients were successfully engrafted with a median time of 20 days (range: 13–40 days) to reach neutrophil levels $>0.5 \times 10^9$/L. Grade I–II aGVHD was diagnosed in 43 (47.8%) patients, while III–IV aGVHD was diagnosed in 12 (13.3%) patients. The majority of patients (52 individuals; 57.8%) had 1 or more episodes of CMV reactivation and received treatment with either ganciclovir or foscarnet sodium.

### Previous IFI characteristics

Details of previous fungal infections and response status at the time of admission for HSCT are shown in Table 2. The previous episodes of fungal infections were graded as proven ($n = 4$), probable ($n = 40$), or possible ($n = 46$). The median time from the diagnosis of primary infection to the time of stem cell infusion was 75 days (range: 24–575 days). Most patients ($n = 87$) had previously experienced lung infections, though infections had also been found in association with liver abscesses ($n = 2$) and in the bloodstream ($n = 1$). Fungal pathogens that had been isolated in conjunction with these infections were *Aspergillus* species ($n = 14$) and *Candida* species ($n = 1$).

All patients responded to antifungal treatment after antibacterial agents failed to have an impact. SCT proceeded once there were no longer any signs of active fungal infection.

**Characteristics of prior invasive fungal infections (IFIs)**

| Characteristic | *n* |
|---|---|
| Diagnosis | |
| Pneumonia | 87 |
| Liver abscess | 2 |
| Bloodstream infection | 1 |
| IFI level | |
| Proven | 4 |
| Probable | 40 |
| Possible | 46 |
| Radiographic abnormality of prior IFI before transplant | |
| Detectable | 56 |
| Undetectable | 34 |
| Time interval between prior IFI and transplant, days | |
| Median (range) | 81 (24–575) |

*Table 2*

### Recurrence rate of IFI under SAP with different agents

Recurrent IFI occurred in 23 of 90 patients (25.5%). Recurrence rates varied according to the antifungal agent used to treat the infection: 2/25 (8%) for voriconazole, 4/23 (17.3%) for itraconazole, 2/7 (28.5%) for caspofungin, 2/7 (28.5%) for micafungin, and 13/28 (46.4%) for fluconazole. Proven fungal infections were found in only 2 of 23 recurrent IFI cases; the remainder were either probable ($n = 16$) or possible ($n = 5$).

The majority of patients experienced lung infections ($n = 22$), though 1 individual suffered from a urinary tract infection. In 8 patients, the site of recurrence was the same as the original infection site. Three fungal pathogens were identified as follows: *Aspergillus* species ($n = 5$), *Mucor* species ($n = 1$), and *Candida* species ($n = 1$). No clear pathogen could be identified in the remaining individuals diagnosed with elevated BG levels.

IFI recurrence treatments included liposomal amphotericin-B ($n = 2$), voriconazole ($n = 15$), itraconazole ($n = 3$), and a combination of caspofungin and 1 of the above drugs ($n = 3$). Salvage treatments controlled infections in all but 1 case.

### Risk factors for IFI recurrence after HSCT

Our univariate analysis revealed that the following parameters had no significant influence on recurrence rates: age, gender, status of the original disease at transplantation, complete resolution of radiographic abnormalities of the prior IFI episode, reactivation of CMV, and donor type (all $P > 0.143$) (Table 3). Variables that influenced the recurrence rate included the following: HLA disparity (34.5% mismatched versus 11.4% fully matched; $P = 0.015$); continuous duration of neutropenia (10.5% $\leq$18 days versus 36.5% >18 days; $P = 0.007$); severity of aGVHD (20.5% grade 0–II versus 58.3% grade III–IV; $P = 0.01$); interval between previous IFI and transplantation (37.5% <70 days versus 16.0% $\geq$70 days; $P = 0.028$); and category of prophylactic drug (46.4% narrow-spectrum [fluconazole] versus 16.10% broad-spectrum; $P = 0.009$) (Table 3).

Our multivariate analysis included the following variables (with a univariate *P*-value <0.25): recipient age, duration of neutropenia, donor type, HLA disparity, presence of grade III–IV aGVHD, interval between primary infection and transplantation, status of original disease at transplantation, and category of prophylactic drug. Only 4 of these were significantly related to

**Results of $\chi^2$ tests assessing risk factors associated with recurrence of invasive fungal infection (IFI) within 100 days of transplantation**

| Factors | *P*-value |
|---|---|
| Gender | 0.775 |
| Age | 0.143 |
| Donor type | 0.23 |
| HLA disparity | **0.015** |
| CR of original disease | 0.228 |
| Interval from prior IFI to HSCT | **0.028** |
| Resolution of abnormalities of prior IFI | 0.461 |
| Duration of neutropenia | **0.007** |
| Presence of grade III–IV GVHD | **0.01** |
| CMV reactivation | 0.671 |
| Spectrum of prophylactic agent | **0.009** |

Bold values are significant.
HLA, human leukocyte antigen; CR, complete remission; HSCT, hematopoietic stem cell transplantation; GVHD, graft-versus-host disease; CMV, cytomegalovirus.

*Table 3*

recurrence rate: duration of neutropenia for >18 days ($P = 0.008$), presence of grade III–IV aGVHD ($P = 0.010$), <70-day interval between previous fungal infection and transplantation ($P = 0.041$), and use of a narrow-spectrum agent (fluconazole) for prophylaxis ($P = 0.001$) (Table 4). The influence of the above variables on the cumulative incidence of IFI recurrence was analyzed by log-rank, as shown in Figure 1.

### Patient outcome at last follow-up

The vast majority of patients (84 individuals; 93.3%) survived until day 100 after HSCT. By the time of the last follow-up on 30 January 2010 (median follow-up period: 551 days; range: 18–1923), 3 patients had dropped out of the study. Of the remaining 87, 60 (69%) were alive and disease-free, 1 (1.2%) was alive but with a tumor, and 26 (29.9%) had died. Only 7 (8.0%) of the deceased patients had died of severe fungal infection; other causes of mortality included relapse of original disease ($n = 10$), severe GVHD ($n = 4$), viral infection ($n = 2$), and organ failure ($n = 2$).

Patients without recurrent IFI had higher survival rates (76.6% versus 52.2%, $P = 0.243$) and lower fungal-related mortality rates (4.7% versus 17.4%, $P = 0.082$) than patients with recurrent IFI, but neither of these differences was significant (Fig. 2).

**Results of logistic regression assessing risk factors associated with recurrence of invasive fungal infection (IFI) within 100 days of transplantation**

| Variable | OR (95% CI) | *P*-value |
|---|---|---|
| Age in years | | |
| ≤30 | 1 | 0.537 |
| >30 | 0.635 (0.15–2.684) | |
| Status of underlying disease | | |
| CR1 | 1 | 0.182 |
| CR2/CR3 | 0.846 (0.163–4.396) | 0.842 |
| NR/REL | 3.658 (0.713–518.756) | 0.120 |
| Donor type | | |
| MSD | 1 | 0.162 |
| URD | 43.366 (0.897–2.098) | 0.057 |
| HRD | 3.605 (0.407–31.938) | 0.249 |
| HLA disparity | | |
| Mismatched | 1 | 0.376 |
| Fully matched | 0.522 (0.124–2.201) | |
| Duration of neutropenia, days | | |
| ≤18 | 1 | **0.008** |
| >18 | 7.301 (1.675–31.831) | |
| Interval between prior IFI and transplant, days | | |
| <70 | 1 | **0.041** |
| ≥70 | 0.258 (0.070–0.947) | |
| Grade III–IV aGVHD | | |
| Absent | 1 | **0.010** |
| Present | 7.691 (1.640–36.060) | |
| Prophylactic agent | | |
| Narrow-spectrum | 1 | **0.001** |
| Broad-spectrum | 0.087 (0.022–0.347) | |

Bold values are significant.
OR, odds ratio; CI, confidence interval; CR, complete remission; NR, no remission; REL, relapse; MSD, matched sibling donor; URD, unrelated donor; HRD, haploidentical-related donor; HLA, human leukocyte antigen; aGVHD, acute graft-versus-host disease.

*Table 4*

## Discussion

Our results confirm that fungal infections are a major problem in allo-HSCT patients with a history of IFI. However, we have been able to determine several risk factors (duration of neutropenia for >18 days, presence of grade III-IV aGVHD, a <70-day interval between previous fungal infection and transplantation, and use of a narrow-spectrum agent for prophylaxis)

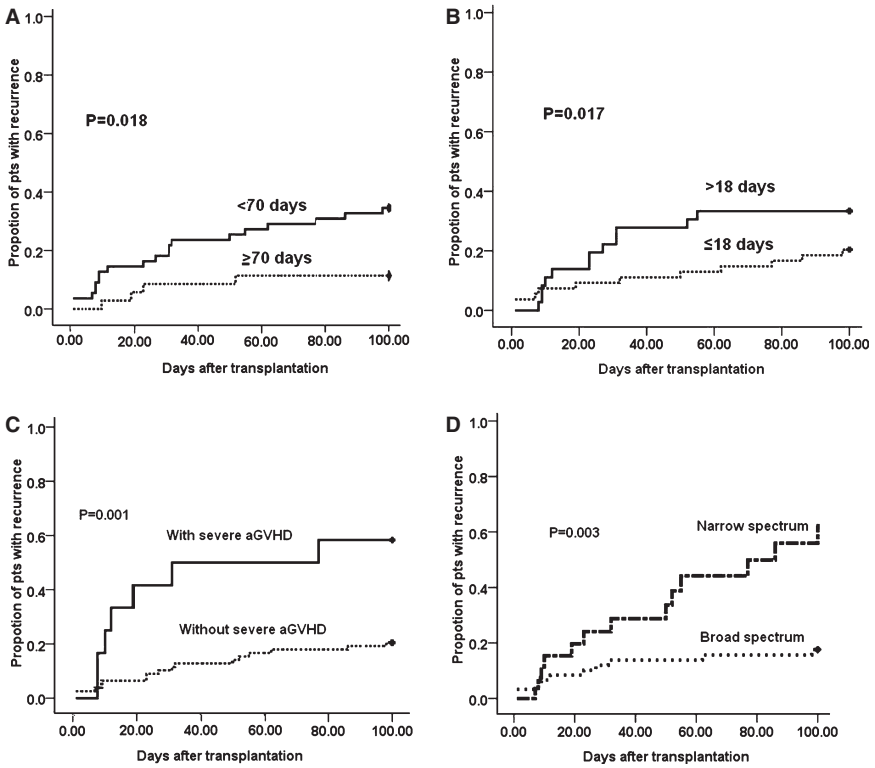


*Fig. 1.* The influence of different variables on invasive fungal infection (IFI) recurrence rate. (A) Interval between prior IFI and current hematopoietic stem cell transplant (HSCT); (B) Duration of neutropenia; (C) Presence or absence of severe acute graft-versus-host disease (aGVHD); (D) Type of antifungal agent. Pts, patients.

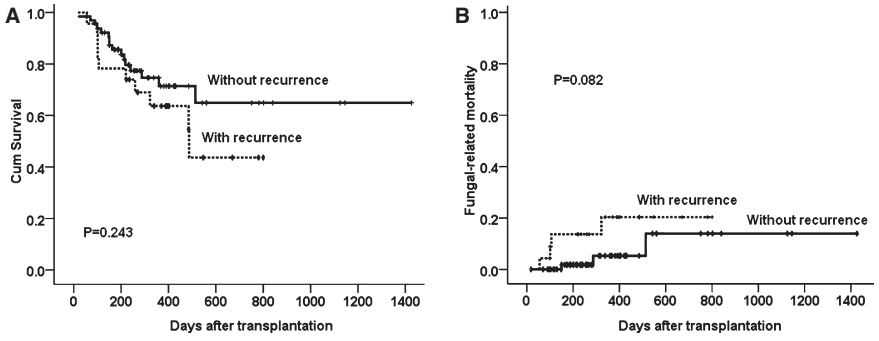


*Fig. 2.* Survival (A) and fungal-related mortality (B) rates in patients with or without invasive fungal infection recurrence.

that can be used to identify which patients are particularly likely to suffer early IFI recurrence after allo-HSCT under SAP. This information should be useful in improving treatment—and, ultimately, survival rates—of allo-HSCT patients.

A variety of antifungal agents have been found to be effective for SAP in allo-HSCT patients; these include voriconazole, itraconazole, caspofungin, and liposomal amphotericin-B (8–12). However, the majority of previous studies have been characterized by small sample sizes and heterogeneous study groups; furthermore, no researchers have made specific recommendations on drug selection. In this study, we considered the identity of the pathogen involved in prior IFI, as well as the efficacy of previously employed antifungal agents, when selecting which drug should be prescribed; we also kept in mind patients' financial capacity and organ function. Our results showed that broad-spectrum

agents, such as voriconazole, itraconazole, caspofungin, and micafungin, were more efficient in SAP than fluconazole. As previously reported by Cordonnier et al. (8, 12), voriconazole was particularly powerful; among our patients, it was also the most efficient, with only an 8% recurrence rate. Unfortunately, our relatively small sample size did not permit us to perform a statistical analysis on differences in recurrence rate relative to the antifungal agent used in SAP. Future work on a larger number of patients will be necessary to further explore which are the best agents for SAP.

Researchers have previously identified a number of risk factors for the development of IFI after HSCT: prior fungal exposure or colonization, state of immunosuppression, status of underlying hematologic disease, GVHD/graft rejection, bacteremia, organ dysfunction, and HLA disparity of the graft and stem cell source (2, 13–17). However, unlike the current study, none of this work has specifically investigated allo-HSCT patients undergoing SAP. Of the many factors analyzed here, only 4 were identified as risk factors for IFI recurrence: prolonged neutropenia (>18 days), a short interval between prior IFI and HSCT (<70 days), the presence of severe aGVHD, and use of a narrow-spectrum prophylaxis agent. Cumulatively, these results suggest that incidence of recurrent IFI—and, therefore, the transplantation outcome—can be improved by adequate antifungal treatment before transplantation, better prevention of, and therapy for, severe aGVHD, use of granulocyte colony-stimulating factor to reduce the duration of neutropenia, and use of broad-spectrum agents for prophylaxis.

A high mortality rate (20–80%) is associated with IFI, particularly in patients experiencing a relapse (3, 4, 18). However, the widespread use of SAP has greatly decreased fungal-related mortality. In the first prospective multicenter clinical trial evaluating voriconazole as an SAP in allo-HSCT recipients with previous proven or probable IFI, Cordonnier et al. (12) reported only a single death from systemic fungal disease, and only a $6.7 \pm 3.6\%$ 1-year cumulative incidence of IFI relapse. Likewise, we observed a 70.1% survival rate in our patients, and a relatively low (8%) fungal-related mortality rate. Because half of our patients were graded as being "possible" cases, we performed a separate analysis including data only from the 44 patients with a previous proven or probable IFI. This subsample of individuals experienced similar early recurrence rates (25%) and IFI-related mortality rates (11.3%). We also found that overall survival rates were higher in patients without recurrent IFI, reflecting the importance of SAP to decrease the risk of recurrence rate and improve overall survival.

The results of our retrospective study suggest that allo-HSCT can be safely and effectively performed in patients with previous IFI. Risk factors for IFI recurrence include prolonged neutropenia (>18 days), a short interval between prior IFI and HSCT ($\leq 70$ days), the presence of severe aGVHD, and use of a narrow-spectrum agent for prophylaxis. This information may help hematologists identify patients at increased risk for IFI recurrence and seek strategies to reduce the risk. Prospective and randomized studies assessing the ideal antifungal agents for SAP are needed in the future.

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*Author contributions*: F.L.: patient management, research design, data analysis, manuscript writing. T.W.: research design, manuscript editing, patient management. All others: patient management.

*Conflict of interest*: The authors have no conflicts of interest to declare.

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