Invasive Fungal Infections While on Voriconazole, Liposomal Amphotericin B, or Micafungin for Antifungal Prophylaxis in Pediatric Stem Cell Transplant Patients

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OBJECTIVE This study aimed to report the incidence of invasive fungal infections (IFIs) in pediatric hematopoietic stem cell transplant (HSCT) patients who received voriconazole, liposomal amphotericin B (L-AMB), or micafungin for primary antifungal prophylaxis (PAP).

METHODS Using data retrospectively collected from institution's electronic records, this study analyzed the incidence of IFIs in pediatric HSCT patients between November 2012 and November 2016.

RESULTS A total of 103 patients were screened. Of the 84 patients who met inclusion criteria, 76.2%, 29.8%, and 19% patients received voriconazole, L-AMB, and micafungin, respectively. The incidence of overall IFIs was 2.08 per 1000 prophylaxis days. There were 2 mold infections identified in 2 patients. Among 3 antifungal agents, the rates of IFIs were 2.67 per 1000 prophylaxis days in L-AMB group, 2.08 per 1000 prophylaxis days in micafungin group, and 1.17 per 1000 prophylaxis days in voriconazole group.

CONCLUSION Patients who received L-AMB or micafungin had higher rates of IFIs than those who received voriconazole for PAP.

ABBREVIATIONS ALT, alanine aminotransferase; AML, acute myeloid leukemia; AST, aspartate aminotransferase; GM, galactomannan; HSCT, hematopoietic stem cell transplant; IDSA, Infectious Diseases Society of America; IFI, invasive fungal infection; IA, invasive aspergillosis; L-AMB, liposomal amphotericin B; PAP, primary antifungal prophylaxis; SCr, serum creatinine

KEYWORDS antifungal prophylaxis; invasive fungal infection; liposomal amphotericin B; micafungin; voriconazole

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Introduction

Invasive fungal infections (IFIs) remain a significant cause of morbidity and mortality in patients undergoing hematopoietic stem cell transplant (HSCT). A major challenge in addressing the complications of IFIs is the difficulty of early diagnosis. *Candida albicans*, *Cryptococcus neoformans*, *Aspergillus fumigatus*, and *Pneumocystis jirovecii* are the most well-known causes of opportunistic mycosis.^{1,2} According to Simms-Waldrup et al,³ the overall incidence of fungal infections in pediatric HSCT recipients was 14.5% at a single institution. Marr et al⁴ reported similar incidences of invasive aspergillosis (IA) and non-*Aspergillus* infection, with a range of 4% to 14% in allogeneic stem cell transplant patients. Among children receiving HSCT, studies prior to 2008 reported 66% mortality, but more recent surveys reported mortality rates vary between 35% and 41%.⁵ Robenshtok et al⁶ conducted a meta-analysis, and concluded that antifungal prophylaxis reduced all-cause mortality, fungal-related mortality, and documented IFI. Therefore, the prompt initiation of antifungal prophylaxis could

improve survival in HSCT patients.

Based on the 2009 American Society for Blood and Marrow Transplantation's Guidelines, voriconazole, posaconazole, or micafungin are acceptable alternative agents compared with the drug of choice fluconazole among HSCT recipients. Studies have shown that these agents are comparable with fluconazole in preventing IFIs.^{7,8} According to the 2010 Infectious Diseases Society of America (IDSA) Clinical Practice Guideline, voriconazole or micafungin may be added to provide *Candida* and *Aspergillus* species coverage in high risk patients, including HSCT recipients.⁹ The 2016 IDSA Guidelines for the Diagnosis and Management of Aspergillosis recommended voriconazole or posaconazole as first line for fungal prophylaxis, and micafungin as an alternative agent in patients with high risk for IA.¹⁰ Similarly, the Infectious Diseases Working Party of the German Society for Hematology and Medical Oncology Guideline also recommended voriconazole or micafungin as the antifungal prophylaxis agent post-HSCT, with the same quality of evidence.¹¹ In a 2016 meta-analysis, Xu et al¹² compared the inci-

dence of IFIs, mortality, and adverse effects in HSCT patients who received voriconazole or micafungin for antifungal prophylaxis. The authors concluded that voriconazole and micafungin were well tolerated with manageable side effects, and most importantly, both agents significantly reduced the prevalence of proven IFIs over fluconazole and itraconazole.¹² This result was consistent with the findings of a meta-analysis conducted by Ethier et al.¹³ Mold-active compared with fluconazole prophylaxis significantly reduced proven/probable IFI, IA, and IFI-related mortality in patients with cancer receiving chemotherapy or HSCT. In contrast, a retrospective cohort study by Gomes et al¹⁴ compared the incidence of IFIs with the use of echinocandins or anti-*Aspergillus* azoles in patients 18 years and older. The study found that the rate of IFIs was significantly higher in the echinocandin group compared with the azole group.¹⁴ Literature reporting the incidence of IFIs between voriconazole, liposomal amphotericin B (L-AMB), and micafungin for primary antifungal prophylaxis (PAP) is lacking in pediatric HSCT patients.

Although micafungin is generally well tolerated, voriconazole and L-AMB's common adverse effects are hepatotoxicity and nephrotoxicity, respectively. In a randomized, open-label study conducted by Oyake et al,¹⁵ there were more adverse events associated with voriconazole (56%) than micafungin (20%) including hepatotoxicity and visual disturbances when used as antifungal therapy in patients with hematological disorders. In a randomized, prospective, open label study in pediatric patients with acute myeloid leukemia (AML), voriconazole was found to be comparable to amphotericin B as an antifungal prophylaxis option with less serious adverse events (voriconazole 6% vs. amphotericin B 30%) and fewer toxicities per patient.¹⁶

Based on current institutional practice, voriconazole is used as the first-line agent for antifungal prophylaxis in HSCT patients. However, if there are any suspected drug interactions or adverse effects from voriconazole, patients are transitioned to L-AMB or micafungin. Additional understanding of safety and efficacy could help guide prescribers in their initial selection of antifungal agents. To that end, the goal is to report the incidence of IFIs in pediatric HSCT patients receiving voriconazole, L-AMB, or micafungin for primary fungal prophylaxis at a pediatric medical center.

Materials and Methods

Study Design and Patients. This was a retrospective cohort study to quantify the incidence of IFIs with PAP usage in patients who received a HSCT between November 2012 and November 2016. All patients younger than or equal to 21 years of age admitted to the stem cell transplant unit and received voriconazole, L-AMB, or micafungin up to 120 days after transplant were included. Patients were excluded if they had history of IFIs or developed IFIs within 7 days of antifungal

prophylaxis agent switch. This study was approved by the University of Texas Southwestern Medical Center Institutional Review Board.

Similar to previously published literature,¹⁴ the primary endpoint was to report the incidence of IFIs per 1000 prophylaxis days in pediatric HSCT patients who received voriconazole, L-AMB, or micafungin for PAP. The secondary endpoints were to identify whether IFIs were due to mold or yeast, and medication adverse effects.

Definition. PAP is defined as an antifungal prophylaxis regimen given to patients posttransplant. IFI is characterized by the European Organization for Research and Treatment of Cancer either as proven, probable, or possible infection. Proven IFI is defined as positive mycological evidence including microscopic analysis, sterile material culture, blood culture, or cerebrospinal fluid serological analysis. Probable IFI is based on a combination of host factors, clinical signs, radiologic features, and mycological evidence either using direct test (i.e., cytology, direct microscopy, or culture) or indirect test (detection of antigen or cell-wall constituents). Possible IFI is the combination of host factors, including clinical signs and imaging findings without mycological evidence.¹⁷ Overall IFIs included total patients with proven, probable, and possible infections. If a patient required a change in regimen, a washout period was implemented and defined as 7 days after antifungal switch.

According to the 2016 IDSA Guidelines for the Diagnosis and Management of Aspergillosis, serum assays for (1→3)- β -D-glucan is recommended for diagnosing IA in high-risk patients such as HSCT population, but it is not specific for *Aspergillus*. Serum and bronchoalveolar lavage *Aspergillus* galactomannan (GM) is recommended as an accurate marker for the diagnosis of IA.¹⁰ *Aspergillus* GM, (1→3)- β -D-glucan serum assays, and chest computed tomography were performed if there was a suspicion for fungal infection. Incidence of IFIs was defined as the number of IFIs divided by the total prophylaxis days during the study period.¹⁴ Liver abnormalities were defined as total bilirubin > 3 mg/dL, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) > 5 times the upper limit of normal. Renal abnormalities were defined as abnormal renal blood tests with elevated serum creatinine (SCr) using the Kidney Disease Improving Global Outcomes Guidelines, or creatinine clearance < 90 mL/min/1.73 m² calculated by Bedside Schwartz in pediatric patients or Cockcroft-Gault in adult patients.¹⁸

Study Population. Patients with HSCT were retrospectively reviewed using electronic medical record. Data were recorded using patient charts in EPIC from November 2012 to November 2016. A total of 103 patients were screened. Nineteen patients (18.4%) were excluded for the following reasons: 17 patients had a history of IFIs, and 2 patients developed IFIs within 7 days of an antifungal change. Eighty-four HSCT patients

Table 1. Patient Demographic and Baseline Characteristics (N = 84 Patients)

Parameters	Baseline at the Start of Transplant (N = 84)	Antifungal Therapy		
		Voriconazole (n = 64)	L-AMB (n = 25)	Micafungin (n = 16)
Sex				
Female, n (%)	32 (38.1)	25 (39.1)	9 (36)	6 (37.5)
Male, n (%)	52 (61.9)	39 (60.9)	16 (64)	10 (62.5)
Age, yr, median (range)	9 (0–21)	9 (0–21)	9 (0–21)	9 (0–19)
Weight, kg, median (range)	33.4 (6.8–115.2)	37.2 (6.8–115.2)	31.7 (14–76.4)	31.3 (6.8–69.3)
SCr, mg/dL, median (range)	0.4 (0.1–2.5)	0.4 (0.1–2.5)	0.4 (0.3–0.7)	0.4 (0.2–0.7)
ALT, units/L, median (range)	27 (8–327)	27 (8–141)	29 (10–219)	23 (12–327)
AST, units/L, median (range)	17 (3–418)	20 (3–115)	15 (5–243)	18 (7–418)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; L-AMB, liposomal amphotericin B; SCr, serum creatinine

were included in the analysis.

Data Collection. Retrospective collection of patients' clinical and demographic data included the following: age, sex, race, weight, height, day of transplant, location of admission; voriconazole, L-AMB, and micafungin dosing regimens; voriconazole serum trough concentration; *Aspergillus* GM; (1→3)-β-D-glucan serum assays; liver function tests (ALT, AST, and total bilirubin); renal function tests (blood urea nitrogen, SCr, and creatinine clearance); culture data; and incidence of IFIs.

Statistical Analysis. A sample size of 172 patients was needed to achieve 90% power to show a significant difference in incidence rate between 2 PAP groups. With 3 PAP groups, this study did not have enough patients to achieve power. Therefore, outcomes were analyzed using descriptive statistics.

Results

Patient Characteristics. Of the 84 patients who met inclusion criteria, 76.2%, 29.8%, and 19% patients received voriconazole, L-AMB, and micafungin, respec-

tively. The median age of patients was 9 years (range, 0–21 years), and 61.9% were male (Table 1). The median weight was 33.4 kg (range, 6.8–115.2 kg) at the start of transplant. Baseline SCr, ALT, and AST were comparable among 3 antifungal prophylaxis groups. No patient received more than 1 prophylaxis therapy at 1 time. There were 24 patients (28.6%) who received an antifungal therapy switch during the study period; the switch was based on physicians' decisions regarding 17 patients who clinically deteriorated, and 7 patients who experienced intolerable adverse events.

IFIs During PAP. Among 84 patients, there were a total of 21 incidences of IFIs during the study period (Table 2). One patient had a positive blood culture with unidentified mold. One patient had a positive serum *Aspergillus* GM level. Both of these patients were in L-AMB group. There was no pattern of resistance identified with this low yield of positive cultures. Five patients (23.8%) had positive serum assays for (1→3)-β-D-glucan.

PAP was administered for a total of 10,080 prophylaxis days. The incidence of overall IFIs was 2.08 per 1000

Table 2. Pattern of PAP Use and Incidence of IFIs (N = 84 Patients)

PAP Drugs	Patients, n (%)	Dosage	Incidence of IFIs, n (%)
Voriconazole* (oral or intravenous)			
Overall	64 (76.2)	8–18 mg/kg/day	9 (14.1)
Only agent given	41 (64)		6 (9.4)
L-AMB†			
Overall	25 (29.8)	3–10 mg/kg weekly	8 (32)
Only agent given	6 (24)		5 (20)
Micafungin‡			
Overall	16 (19)	1–3 mg/kg/day	4 (25)
Only agent given	5 (31.3)		1 (6.3)

IFI, invasive fungal infections; L-AMB, liposomal amphotericin B; PAP, primary antifungal prophylaxis

* Starting dose range from 4–9 mg/kg/dose twice daily; dose range from 100 to 400 mg twice daily during the study period; dose was adjusted based on voriconazole serum trough concentration.

Figure. Incidence of invasive fungal infections per 1000 prophylaxis days during voriconazole, L-AMB, or micafungin as primary antifungal prophylaxis.

L-AMB, liposomal amphotericin B

prophylaxis days. Molds accounted for 9.5% of total IFIs with an incidence rate of 0.2 per 1000 prophylaxis days (Table 2). The remaining IFIs were culture-negative with direct or indirect mycological evidence, or based on combination of host factors. Patients who received L-AMB (2.67 per 1000 prophylaxis days) and micafungin (2.08 per 1000 prophylaxis days) had higher rates of IFIs than those who received voriconazole (1.17 per 1000 prophylaxis days) as PAP (Figure). There was 1 proven IFI in L-AMB group; all other IFIs were probable and possible. In the voriconazole and micafungin groups, the majority were categorized as possible IFIs. In the L-AMB group, the majority were probable IFIs (Table 3).

Adverse Events. L-AMB and micafungin groups had higher rate of liver and renal abnormalities compared with voriconazole. Liver abnormalities were observed in 35.9%, 76%, and 81.3% patients who received voriconazole, L-AMB, and micafungin group, respectively. Renal abnormalities developed in 54.7%, 84%, and 62.5% patients in voriconazole, L-AMB, and micafungin group, respectively (Table 4).

Discussion

Based on previously published literature, the incidence of IFIs in pediatric HSCT recipients is estimated to be 8% to 17%.¹ Although antifungal prophylaxis is an effective strategy to reduce IFIs in patients with stem

cell transplantation, the choice of antifungal prophylaxis agent still remains controversial.^{19,20} This retrospective, single-center study found that the use of L-AMB or micafungin as PAP had higher incidences of IFIs when being compared with voriconazole. To account for confounding variables, this study excluded patients who developed IFIs within 7 days of an antifungal switch to allow time to clear the previous antifungal agent, and time to steady state of the newly added antifungal agent. This study is the first to describe the incidence of IFIs in pediatric patients after stem cell transplantation using incidence rate per 1000 prophylaxis days.

In pediatric populations, PAP therapy selection is primarily extrapolated from adult evidence that include retrospective cohorts, prospective studies, meta-analysis, and published guidelines.^{7,9,10} In a 2014 review by Pechlivanoglou et al,²¹ IFI prophylaxis had a positive effect on risk reduction compared with no prophylaxis in adult patients with HSCT or hematological malignancies. In addition, a meta-analysis from 1996 to 2013 found that using voriconazole or micafungin as antifungal prophylaxis had a lower risk of IFIs than the narrower spectrum agents such as fluconazole or itraconazole in adult patients with HSCT.¹² Therefore, voriconazole or micafungin seem to be reasonable agents for antifungal prophylaxis because of their mold coverage.

In this study, voriconazole is the antifungal agent of choice with routine therapeutic drug monitoring. Voriconazole serum trough level is obtained on day 5 of therapy initiation and dose adjustments are subsequently made. Due to voriconazole's unpredictable pharmacokinetics and many drug interactions, this study could not rule out that some breakthrough IFIs were due to suboptimal drug exposure. Six out of nine (66.7%) patients who developed IFIs had subtherapeutic voriconazole troughs (< 1 mg/L) when IFI was diagnosed, and therapeutic troughs concentrations (1–2 mg/L)^{22–28} were achieved in patients who did not develop IFIs. Potentially, the overall incidence of IFIs and incidences of IFIs in voriconazole group could have been lowered if all patients had therapeutic voriconazole serum trough levels for prophylaxis.

For situations in which voriconazole is not an ideal

Table 3. Incidence of IFIs During Voriconazole, L-AMB, or Micafungin as PAP (N = 84 Patients)

IFIs Outcomes, n (rate)	Incidence of IFIs* During PAP (per 1000 Prophylaxis Days)		
	Voriconazole (n = 64)	L-AMB (n = 25)	Micafungin (n = 16)
Overall	9 (1.17)	8 (2.67)	4 (2.08)
Proven	0 (0)	1 (0.33)	0 (0)
Probable	1 (0.13)	4 (1.33)	1 (0.52)
Possible	8 (1.04)	3 (1)	3 (1.56)

EORTC, European Organization for Research and Treatment of Cancer; IFIs, invasive fungal infections; L-AMB: liposomal amphotericin B; PAP, primary antifungal prophylaxis

* Revised EORTC criteria for proven, probable, and possible IFIs.

Table 4. Adverse Events of Voriconazole, L-AMB, or Micafungin Use as Primary Antifungal Prophylaxis (N = 84 Patients)

Outcomes, n (%)	Voriconazole (n = 64)	L-AMB (n = 25)	Micafungin (n = 16)
Liver abnormalities*	23 (35.9)	19 (76)	13 (81.3)
Renal abnormalities†	35 (54.7)	21 (84)	10 (62.5)

L-AMB, liposomal amphotericin B

* Abnormal liver blood tests with serum alanine aminotransferase and/or aspartate aminotransferase levels > 5 times the upper limit of normal and/or total bilirubin level > 3 mg/dL.

† Abnormal renal blood tests with elevated serum creatinine based on Kidney Disease: Improving Global Outcomes Guidelines or creatinine clearance < 90 mL/min/1.73 m² calculated by Bedside Schwartz in patients < 18 yr old or Cockcroft-Gault in patients ≥ 18 yr old.

antifungal agent, micafungin can be used. Micafungin is an echinocandin agent that exhibits activity against *Candida* and *Aspergillus* species.^{29,30} In HSCT patients, the dosage of micafungin for prophylaxis in patients weighing less than 50 kg varied from 1 to 3 mg/kg/day, with a maximum of 50 mg/day.^{31–33} The advantages of micafungin over voriconazole and L-AMB include fewer drug interactions, lower risk of liver injury, more predictable pharmacokinetics, and lower adverse events profiles.¹² However, Gomes et al¹⁴ reported that echinocandin-based PAP was found to have higher rates of documented IFIs than anti-*Aspergillus* azoles in adult patients with AML.

With azoles' numerous drug interactions and echinocandins' daily intravenous administration, this current institutional practice uses high-dose weekly L-AMB as one of the antifungal prophylaxis options.³⁴ Based on previous kinetic studies, L-AMB at 10 mg/kg/dose was well tolerated and achieved maximum serum concentration, area under the curve, sufficient plasma, and tissue concentrations 7 days after an infusion.^{35–37} El Cheikh et al³⁸ found that once-weekly L-AMB significantly lowered incidence of IFIs and fungal infection-related mortality compared with azole and echinocandin-based PAP in adults with graft-versus-host disease post-HSCT. The choice of a second-line PAP agent is dependent on medication adverse events, patients' conditions, and physicians' decisions.

These findings provided similar results compared with a study performed in adult patients with AML. Gomes et al¹⁴ reported that patients who received echinocandin-based PAP experienced higher rates of IFIs than those who received anti-*Aspergillus* azoles. Overall, these findings support the first-line choice of voriconazole in pediatric HSCT patients in this institutional practice. The higher incidence of IFIs in the micafungin and L-AMB groups could be attributed to the restricted antifungal coverage and penetration into some sites of infection when compared with voriconazole. However, the incidence of IFI among these 3 antifungal groups could have been affected by multiple factors, including degree of immunosuppression, type of transplant, or environmental exposures. The incidence of overall IFIs identified in this study was higher than results documented in previous pediatric HSCT

studies. In addition, there were 2 patients with IFIs who were excluded because IFIs developed within the 7-day washout period. Both patients were started with voriconazole and transitioned to L-AMB. Mold and yeast IFIs remain a significant issue in this high-risk population. In the past 2 decades, the increasing rates of infection caused by *Aspergillus*, azole-resistant yeasts, and echinocandin-resistant yeasts have been increasingly reported. Overuse of PAP may allow the selection of more resistant organisms. Among the L-AMB group, this study was able to identify only 1 unidentified mold from blood culture as a cause of breakthrough IFI. However, the exact incidence of various molds and yeasts in this study is uncertain as evidence of infection was based on (1→3)-β-D-glucan and *Aspergillus* GM serum assays, which can have a high false positive rate with the concurrent usage of immunoglobulin, B-lactam antibiotics, or blood products.^{39–41}

This retrospective, single-center study had several limitations such as small sample size and lack of power to detect a difference. Additional limitations include absence of information on concomitant drugs, drug interactions, and data comparing pre- and postengraftment phase. High rate of renal and liver abnormalities may be related to the concomitant use of nephrotoxic drugs, hepatotoxic drugs, or drug interactions via the cytochrome P450 system.⁴² In addition, factors that could lead to false positive (1→3)-β-D-glucan and *Aspergillus* GM results were not reported. Extrapolation of these findings to other medical centers may differ based on the differences in epidemiology of IFIs and antifungal selection. Furthermore, this retrospective study was not powered to show statistically significant differences between different antifungal prophylaxis groups, but to report the incidence of IFIs in HSCT patients at a pediatric medical center. Prospective studies are needed to confirm these findings.

Conclusion

In summary, IFI is a continual cause of morbidity and mortality in HSCT recipients despite the broad use of PAP. Prophylaxis with voriconazole was found to have a lower rate of IFIs compared with micafungin and L-AMB in children with HSCT.

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