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TRANSPLANT INFECTIOUS DISEASE

ORIGINAL ARTICLE

Optimizing antifungal prophylaxis in allogeneic stem cell transplantation: A cohort study of two different approaches

Philip R. Selby[1,2] | Morgyn S. Warner[1,3,4] | Sandra L. Peake[1,5] | Peter Bardy[1,6] | Devendra Hiwase[1,4,6,7] | Deepak Singhal[1,4,6,7] | Ashanka Beligaswatte[6,8] | Uwe Hahn[1,4,6] | Jason A. Roberts[9,10,11,12] | David Yeung[1,4,6,7] | Sepehr Shakib[1,13]

[1]School of Medicine, University of Adelaide, Adelaide, South Australia, Australia

[2]Pharmacy Department, Royal Adelaide Hospital, Adelaide, South Australia, Australia

[3]Infectious Diseases Unit, Royal Adelaide Hospital, Adelaide, South Australia, Australia

[4]SA Pathology, Adelaide, South Australia, Australia

[5]Department of Intensive Care Medicine, The Queen Elizabeth Hospital, Adelaide, South Australia, Australia

[6]Haematology Unit, Royal Adelaide Hospital, Adelaide, South Australia, Australia

[7]Cancer Theme, South Australian Health and Medical Research Institute, Adelaide, South Australia, Australia

[8]College of Medicine and Public Health, Flinders University, Adelaide, South Australia, Australia

[9]University of Queensland Centre for Clinical Research, Faculty of Medicine, The University of Queensland, Brisbane, Queensland, Australia

[10]Herston Infectious Diseases Institute (HeIDI), Metro North Health, Brisbane, Queensland, Australia

[11]Department of Pharmacy and Intensive Care Medicine, Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia

[12]Division of Anaesthesiology Critical Care Emergency and Pain Medicine, Nîmes University Hospital, University of Montpellier, Nîmes, France

[13]Department of Clinical Pharmacology, Royal Adelaide Hospital, Adelaide, South Australia, Australia

Correspondence
Philip R. Selby, Pharmacy Department, Royal Adelaide Hospital, Adelaide, SA, Australia.
Email: Philip.Selby@sa.gov.au

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Abstract

Background: Limited consensus exists on the optimal use of antifungal agents to prevent invasive fungal infection in the early post allogeneic hematopoietic stem cell transplant (alloHCT) period, particularly when patients cannot tolerate oral medication administration.

Methods: We undertook a retrospective observational cohort study to assess the tolerability, efficacy, and cost of a new antifungal prophylaxis pathway at a major tertiary alloHCT centre. Patients aged ≥16 years who underwent alloHCT between February 2018 and October 2019 (cohort 1) or between April 2020 and November 2021 (cohort 2) were included. In both cohorts, first line prophylactic therapy was oral posaconazole. The second line drugs where oral therapy was unable to be administered were intravenous voriconazole (cohort 1) versus intravenous posaconazole (cohort 2).

Abbreviations: alloHCT, allogeneic hematopoietic stem cell transplantation; AUD, Australian dollar; BAL, bronchoalveolar lavage; CI, confidence interval; C_{min}, trough concentration; CTCAEv5, common terminology and criteria for adverse events version 5; GVHD, graft versus host disease; IFI, invasive fungal infection; IV, Intravenous; LAmB, liposomal amphotericin B; OR, odds ratio; PO, oral; SD, standard deviation; SUS, suspension; TAB, tablets.

Results: There were 142 patients enrolled in the study, 71 in each cohort. The proportion of patients remaining on first-line prophylaxis or progressing to second-, third-, and fourth-line options was 22.5%, 39.4%, 29.6%, and 8.5% in cohort 1 and 39.4%, 59.2%, 1.4%, and 0% in cohort 2, respectively. The frequency of neuropsychiatric adverse events was significantly higher in cohort 1 compared to cohort 2 (49.3% vs. 19.8%, $p = .0004$). Occurrence of proven and probable fungal infections was not significantly different between cohorts. Antifungal drug expenditure was $359 935 (AUD) more in cohort 1 ($830 486 AUD) compared to cohort 2 ($477 149 AUD).

Conclusion: The antifungal prophylaxis pathway used in cohort 2 resulted in reduced antifungal-associated adverse effects, less patients requiring progression to 3rd and 4th line prophylaxis and reduced antifungal drug costs.

KEYWORDS
allogeneic stem cell transplantation, antifungal prophylaxis, invasive fungal infection, posaconazole, voriconazole

1 | INTRODUCTION

Invasive fungal infection (IFI) represents a significant cause of morbidity and mortality in the allogeneic hematopoietic stem cell transplant (alloHCT) population, with a 12-month cumulative IFI incidence of approximately 6%–17% and comprising 14% of infection-related.[1–3] Numerous factors place this patient group at risk of both invasive yeast and mould infections: including prolonged periods of neutropenia, gastrointestinal tract mucositis, and impaired humoral plus cellular immunity.[4,5] Various strategies to prevent IFIs including prophylaxis or pre-emptive treatment involving different antifungal agents are employed; however, there is limited uniformity between different transplant centers around the world.[4]

Current agents utilized for antifungal prophylaxis in alloHCT include azoles such as fluconazole, itraconazole, voriconazole and posaconazole, echinocandins, and liposomal amphotericin B (LAmB).[4,6,7] Due to its broad spectrum of activity, the availability of oral (tablet and suspension) and intravenous formulations and good tolerability, posaconazole is one of the more common agents used for antifungal prophylaxis in the early alloHCT setting.[6,8,9] The use of posaconazole for IFI prophylaxis has demonstrated improved survival in patients with acute myeloid leukemia and a reduction in IFI-related death in alloHCT patients with graft versus host disease (GVHD).[10,11] Interestingly, guidelines and transplant centers have often extrapolated this evidence to recommend use in the pre-engraftment or early postengraftment (but no GVHD) setting despite a lack of randomized controlled trials.[6,8,9,12,13] Generally, the use of mould-active antifungal prophylaxis in the early alloHCT period is differentiated based on the risk of mould infections. The current Australian and New Zealand guidelines recommend posaconazole as first line antifungal prophylaxis for alloHCT patients at high risk (>10% incidence) of IFI [8], with evidence mostly from network meta-analyses and observational cohort studies.[14–18] The European Conference on Infections in Leukaemia (ECIL) guidelines currently suggest antifungal prophylaxis in the pre-engraftment phase with fluconazole for centres with a low incidence (<5%) of mould infections while voriconazole and itraconazole were the agents receiving the strongest recommendations, where the risk of mould infections is high.[19] The American Society of Clinical Oncology/Infectious Diseases Society of America guidelines suggest a mould active triazole be used if the risk of invasive aspergillosis is >6%.[20]

While the intent of such consensus statements is clear, the optimal strategies to maximize coverage and minimize toxicity are not well established. In particular, there is limited guidance on how to manage the practical difficulties of antifungal administration and associated toxicities, and cost implications in this patient group.[8,9,21] A formal audit of our institutional practice on antifungal prophylaxis for alloHCT patients in 2019/2020 found that patients frequently required antifungal drug changes as a result of antifungal-associated toxicity. This prompted a formal change in our antifungal prophylaxis algorithm and subsequent data collection to assess the effectiveness of our intervention. Here, we report outcomes of our new antifungal prophylactic strategy, with the cohort prior to the change used as a historical control.

2 | METHODS

We performed a retrospective observational cohort study at the Royal Adelaide Hospital Haematopoietic Stem Cell transplant unit, a major metropolitan tertiary care centre, where approximately 50 alloHCT procedures are performed each calendar year. Ethics approval was obtained from the institution's local ethics committee. Patients were included in the study if they were undergoing alloHCT during the specified time periods mentioned and were ≥16 years old. There were no reasons for patients to be excluded from the study.

The retrospective analysis included 71 consecutive alloHCT patients treated from February 2018 until October 2019 (cohort 1). These patients underwent alloHCT with a well-defined set of prophylactic antifungal guidelines (period 1, Appendix 1). Briefly, the first, second, third-, and fourth-line options used were posaconazole modified release tablets, intravenous voriconazole, intravenous LAmB, and intravenous posaconazole. Patients progressed down the list in sequential order when they encountered issues with medication administration, treatment-related toxicity, or reduced efficacy as evidenced by clinical or pharmacokinetic parameters that may imply inadequate target serum levels.

In March 2020, our institutional antifungal prophylaxis guidelines were updated (period 2, Appendix 2) to minimize antifungal-associated toxicity and to decrease the changes in antifungal agent due to intolerance. The new guideline recommended use of intravenous posaconazole as the preferred agent in patients unable to tolerate an oral formulation. The remainder of the guidelines remained similar to the previous version. Data were then retrospectively collected in another 71 consecutive patients treated between April 2020 and November 2021 to assess the effectiveness of this intervention (cohort 2). A gap existed between the 2 cohorts (November 2019–March 2020) to allow for familiarization and full implementation of the new guideline. The differences in the length of time periods and time of the year between the cohorts were due to the need to analyze a similar number of patients.

The primary outcomes assessed were the tolerability, efficacy, and cost of the antifungal prophylaxis regimens. Tolerability was determined by frequency of idiosyncratic toxicities that required a change in prophylactic antifungal (measured by frequency of occurrence and likelihood of association of antifungal adverse events). The decision to change antifungal secondary to toxicity was made by the treating clinicians based on the individual assessment of each patient. Efficacy was measured by the frequency of probable and proven fungal infections. Cost was measured by antifungal drug expenditure of the two cohorts calculated using actual cost per milligram administered. The drug pricing used for both cohorts was based on actual procurement costs as of April 2020 (the start of cohort 2 time period) to ensure consistency in calculation of cost in both groups. A secondary outcome of requirement for escalation to antifungal treatment was used as a further measure of efficacy. Escalation of antifungal therapy was defined as either (i) change from prophylactic to therapeutic intent for posaconazole or voriconazole, (ii) initiation of an echinocandin, and (iii) initiation of treatment dose LAmB (≥3 mg/kg every 24 h).

Medical records for all patients were reviewed by a single reviewer (PS) for the entirety of their admission for alloHCT. Data collected included baseline demographics and clinical parameters relevant to transplant outcomes, such as pathology results, antifungal administration details, potential antifungal-associated adverse effects, and concomitant medications. Reasons for changes of antifungal agent or route of administration were determined from documentation in patient case notes. Possible, probable, or proven fungal infection was determined as per the current EORTC/MSGERC guidelines.[22] Adverse effects except for hepatotoxicity were graded according to the common terminology and criteria for adverse events version 5 (CTCAEv5).[23] Hepatoxicity was determined and graded as per drug-induced liver injury criteria.[24] The likelihood of adverse events having occurred due to an antifungal agent was determined by the Naranjo criteria.[25] Regular therapeutic drug monitoring of both posaconazole and voriconazole was performed; target concentrations are defined in the appendices. Statistical analysis was performed using GraphPad Prism version 9.0.0 for Windows, GraphPad Software, San Diego, CA, USA. Parametric tests were used for analysis of normally distributed scale variables; otherwise nonparametric tests were performed. A two-sided p value of less than .05 was set to indicate statistical significance. Odds ratios with a 95% confidence interval were calculated in the comparison of outcomes, with statistical significance shown if the confidence interval did not include 1.

3 | RESULTS

Each cohort contained 71 patients. The median (range) age was 54 (16–69) and 51 (17–71) years in cohorts 1 and 2, respectively, p = .53. Acute myeloid leukemia was the most common indication for alloHCT in both groups. Detailed baseline characteristics of the groups are shown in Table 1. The only significant differences identified in baseline characteristics between the groups were an increased number of myelofibrosis patients in cohort 1 and an increased number of patients in cohort 2 receiving the fludarabine 150/busulfan 6.4 conditioning regimen. As these numbers were small, adjustment for these differences or matching was deemed not to be required. Other important factors associated with admission and susceptibility to fungal infection were also considered. The median (range) length of stay in cohort 1 was 30 (15–130) days and 27 (7–158) days in cohort 2 with the difference not reaching statistical significance, p = .075. There was also no significant difference in the median (range) number of days of severe neutropenia per patient (defined as absolute neutrophil count $<0.5 \times 10^9$/L) between cohort 1; 19 (10–38) and cohort 2; 20 (7–61), p = .84.

A detailed comparison of outcomes is shown in Table 2.

3.1 | Tolerability

The contribution of each antifungal agent and formulation to total antifungal use in the two groups is shown in Figure 1. In cohort 1, 16 of 71 (23%) patients remained on first line antifungal prophylaxis throughout their admission as compared with 28/71 (39%) in cohort 2 (p = .045, odds ratio [OR] = 0.45, 95% confidence interval [CI] 0.22–0.94). Progression to the third- and fourth- line antifungal prophylaxis options was significantly greater in cohort 1 (27/71, 38%) as compared with cohort 2 (1/71, 1%), (p < .0001, OR = 44, 95% CI 7.5–458.5). There were also increased overall total changes between antifungal agent and route of administration in cohort 1 (n = 175) compared to cohort 2 (n = 96). While more patients required a change in antifungal therapy due to inability to tolerate oral administration in cohort 1 (51/71, 72%)

TABLE 1 Comparison of baseline characteristics

	Cohort 1	Cohort 2	Significance (*p*-Value)
***Age (years)**, median* (range)	54 (16–69)	51 (17–71)	.53
Sex, n (%)			
Male	45 (63)	40 (56)	.49
Female	26 (37)	31 (44)	.49
***Height (cm)**, median (range)*	171 (151–192)	171 (142–192)	.66
***Total body weight (Kg)**, median (range)*	81.4 (49.5–157.4)	78 (53.9–183)	.45
***BMI (Kg/m^2)**, median (range)*	27.7 (17.6–47.2)	26 (19.4–58.4)	.55
Haematological diagnosis, n (%)			
Acute myeloid leukemia	28 (33)	33 (46)	.5
Acute lymphoblastic leukemia	9 (13)	16 (23)	.19
Myelodysplastic syndrome	12 (17)	7 (10)	.32
Myelofibrosis	9 (13)	1 (1)	.017
Chronic lymphocytic leukemia	2 (3)	1 (1)	>.99
Hodgkin's lymphoma	2 (3)	3 (4)	>.99
Non-Hodgkin's lymphoma	2 (3)	2 (3)	>.99
Aplastic anemia	1 (1)	2 (3)	>.99
Acute undifferentiated leukemia	4 (6)	1 (1)	.37
Other	2 (3)	5 (7)	.44
Stem cell Source, n (%)			
Matched sibling donor[†]	14 (20)	18 (25)	.55
Matched unrelated donor[†]	43 (61)	34 (48)	.18
Umbilical cord blood donor	9 (13)	8 (11)	>.99
Haploidentical donor	5 (7)	11 (15)	.18
Conditioning intensity, n (%)			
Myeloablative conditioning (MAC)	17 (24)	15 (21)	.84
Intermediate intensity Conditioning (MIDI)	8 (11)	8 (11)	>.99
Reduced intensity conditioning (RIC)	46 (65)	48 (68)	.86
Conditioning regime, n (%)			
Cyclophosphamide 120/Busulfan 12.8	9 (13)	8 (11)	>.99
Cyclophosphamide 120/TBI 12Gy	4 (6)	4 (6)	>.99
Fludarabine 150/Melphalan 140	36 (51)	24 (34)	.061
Fludarabine 150/Busulfan 6.4	1 (1)	8 (11)	.033
Fludarabine 150/Cyclophosphamide 60/Thiotepa/TBI 4Gy	8 (11)	8 (11)	>.99
Fludarabine 150/Cyclophosphamide/TBI 2 Gy (Haploidentical)	5 (7)	9 (13)	.4
Other	8 (11)	10 (14)	.8
Antithymocyte globulin, n (%)	42 (59%)	32 (45%)	.13
Baseline creatinine clearance[‡] ***(ml/min), mean (±SD)***	86.6 (±29.3)	94.2 (±32.9)	.18
HCT-CI[§] ***score, n (%)***			
0	27 (38)	23 (32)	.6
1	13 (18)	7 (10)	.23
2	9 (13)	15 (21)	.26
3	10 (14)	13 (18)	.65
>3	12 (17)	13 (18)	.83
Overall median (range)	1 (0 - 6)	2 (0 - 8)	.35

(Continues)

TABLE 1 (Continued)

	Cohort 1	Cohort 2	Significance (*p*-Value)
Previous invasive fungal infection[¶]***, n (%)***			
Nil	62 (87)	68 (96)	.13
Possible	6 (8)	2 (3)	.27
Probable	2 (3)	1 (1)	>.99
Proven	1 (1)	0 (0)	>.99
Antifungal prophylaxis prior to transplant, n (%)			
Yes	53 (75)	55 (77)	.84
No	18 (25)	16 (23)	.84

Abbreviation: SD, standard deviation.

[†]All siblings and unrelated donors are matched 10/10 for HLA-A, -B, -C, -DR, and -DQ; occasional patients have permissive mismatches at HLA-DP as per international best practice.

[‡]Calculated using the Cockcroft–Gault formula.[35]

[§]The Hematopoietic cell transplantation-specific comorbidity index.[36]

[¶]Classified as per current EORTC/MSGERC guidelines.[22]

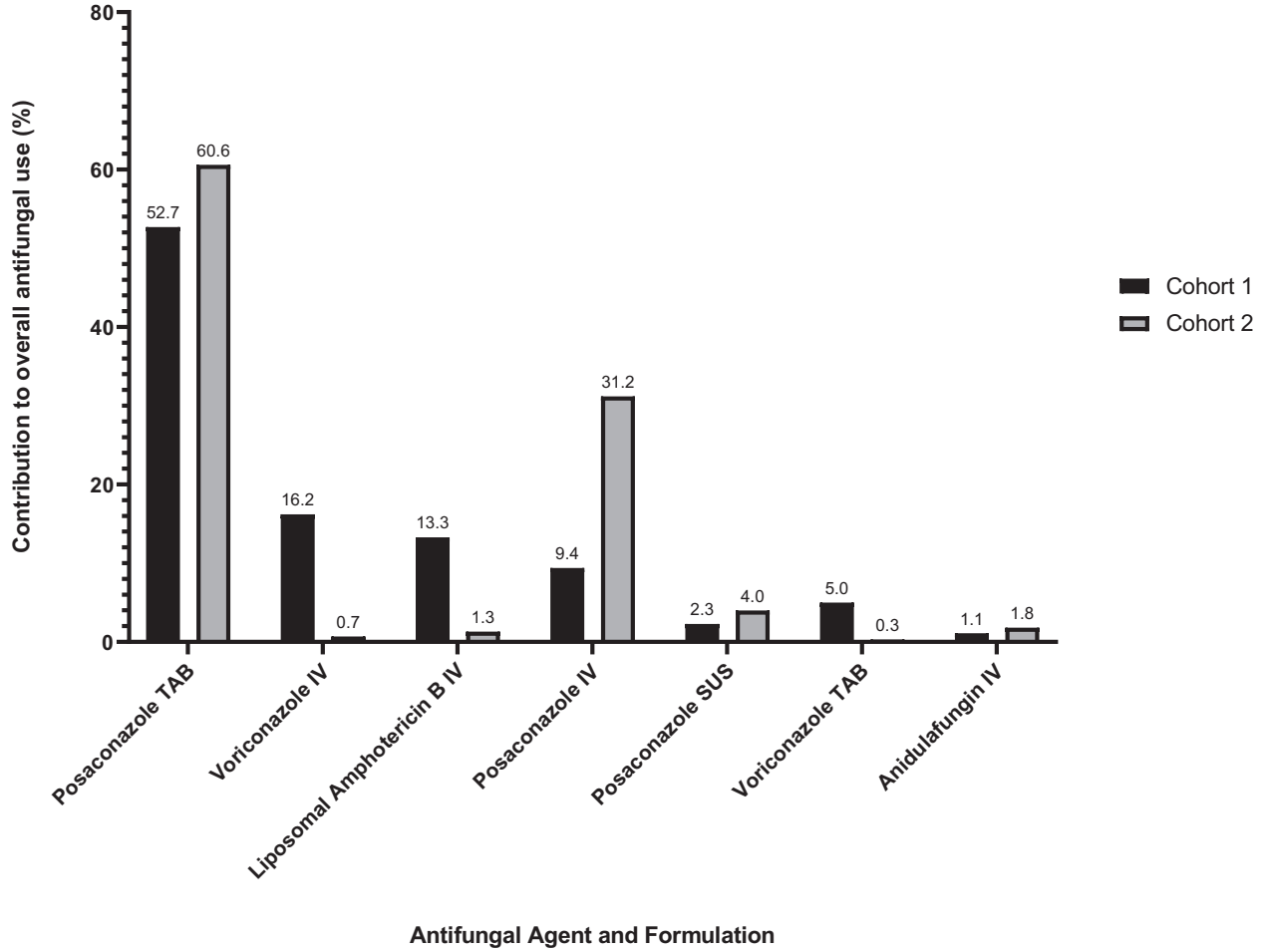

FIGURE 1 Make up of antifungal use in both cohorts. See in separate submitted file.
Abbreviations: IV, intravenous; SUS, suspension; TAB, tablets

TABLE 2 Comparison of outcomes

	Cohort 1	Cohort 2	Significance (*p*-Value)	Odds ratio/95% confidence interval
Antifungal Use				
Number of lines of antifungal prophylaxis per patient, n (%)				
1	16 (23)	28 (39)	.045	0.45 (0.22–0.94)
2	28 (39)	42 (59)	.029	0.45 (0.23–0.89)
3	21 (30)	1 (1)	<.0001	29.4 (4.9–310)
4	6 (8)	0 (0)	.028	-
Total changes in antifungal agent or route of administration (n)	**175**	**96**	-	-
Reason for patients requiring change in antifungal therapy or route of administration				
Oral route unavailable[†] n (%)	51 (72)	42 (59)	.16	1.76 (0.88–3.36)
Escalation to treatment antifungal n (%)	26 (37)	9 (13	.0016	3.98 (1.71–9.42)
Neuropsychiatric toxicity n (%)	20 (28)	0 (0)	<.0001	-
Hepatotoxicity n (%)	2 (3)	2 (3)	>.99	1 (0.15–6.52)
Nephrotoxicity n (%)	7 (10)	0 (0)	.013	-
Physician choice n (%)	2 (3)	1 (1)	>.99	2.03 (0.23–29.77)
Adverse Events				
Neuropsychiatric adverse events – total, n (%)	**35 (49)**	**14 (20)**	**.0004**	**3.96 (1.87–8.03)**
Visual Hallucinations[‡], n (%)	21 (30)	3 (4)	<.0001	9.52 (2.88–31.18)
Delirium[‡], n (%)	14 (20)	11 (15)	.66	1.34 (0.55–3.1)
Probably due to antifungal[§], n (%)	19 (26)	0 (0)	<.0001	-
Nephrotoxicity: Patients experiencing acute kidney injury ≥ grade 2[†] - total, n (%)	**44 (62)**	**36 (51)**	**.24**	**1.58 (0.8–3.04)**
Hepatotoxicity: Patients experiencing potential Drug Induced Liver Injury[¶], n (%)	**22 (31)**	**15 (21)**	**.25**	**1.68 (0.80–3.47)**
Invasive fungal infections				
Proven[††], n (%)	**2 (3)**	**5 (7)**	**.44**	**0.38 (0.07–1.89)**
Probable[††], n (%)	**3 (4)**	**1 (1)**	**.62**	**3.09 (0.45–40.61)**
Possible[††], n (%)	**20 (28)**	**3 (4)**	**.0002**	**8.89 (2.67–29.2)**
Antifungal drug costs				
Overall drug cost (AUD)	**830 486**	**477 149**	-	-
Drug cost per day of admission (AUD)	**238.20**	**154.47**	-	-
Drug cost per patient (AUD)	**11 697**	**6 720**	-	-

Abbreviations: AUD, Australian Dollar; IFI, invasive fungal infection.
[†]Due to either mucositis, nausea, or clinicians' assessment that absorption from the gastrointestinal tract was potentially unreliable.
[‡]As per common terminology and criteria for adverse events - version 5 criteria.[23]
[§]As per Naranjo Criteria.[25]
[¶]As per drug induced liver injury (DILI) criteria.[24]
[††]Classified as per current EORTC/MSGERC guidelines.[22]

compared to cohort 2 (42/71, 59%), the difference was not statistically significant, ($p = .16$, OR = 1.76, 95% CI 0.88–3.46). This was the most common reason for change of therapy in both cohorts and was due to either mucositis, nausea, or clinicians' assessment that absorption from the gastrointestinal tract was potentially unreliable.

Rates of neuropsychiatric adverse events occurred at a significantly greater frequency in cohort 1 as compared to cohort 2 (35/71 vs. 14/71, 49% vs. 20% respectively, $p = .0004$; OR = 3.96, 95% CI 1.87–8.03). Specifically, this was due to a difference in the occurrence of visual hallucinations; 21/71 (29%) in cohort 1 compared to 3/71 (4%) in cohort 2 ($p < .0001$, OR = 9.52, 95% CI 2.88–31.18). There was no significant difference in the occurrence of delirium in cohort 1 (14/71, 20%) and cohort 2 (11/71, 15%) ($p = .66$, OR = 1.34, 95% CI 0.55–3.1). Neuropsychiatric adverse events were determined to be probably due to the antifungal in 19/35 (54%) cases in cohort 1 and in 0/14 (0%) cases in cohort 2 (p <.0001). In all 19 occurrences in cohort 1, the associated antifungal was voriconazole. Nine of the 26 patients who experienced neuropsychiatric events on voriconazole did not have a trough serum concentration available as the drug was ceased prior to samples being obtained. None of the other 17 patients had a trough voriconazole concentration that would be deemed supratherapeutic (>5.5 mg/L).

There was no significant difference in the occurrence of ≥grade 2 acute kidney injury between the groups overall; cohort 1 = 44/71 (62%), cohort 2 = 36/71 (51%) (p = .24, OR = 1.58, 95% CI 0.8–3.04). In cohort 1, a change in antifungal therapy occurred due to nephrotoxicity on seven occasions, with LAmB being the agent that was discontinued in all cases. There were no antifungal changes secondary to nephrotoxicity in cohort 2.

3.2 | Efficacy

The rate of proven infections in cohorts 1 and 2 was 2 of 71 (3%) and 5 of 71 (7%), respectively, p = .44. Probable infections occurred at a rate of 3 of 71 (4%) in cohort 1 and 1 of 71 (1%) in cohort 2, p = .62. The details of proven and probable infections are provided in Table S1. There were significantly more patients in cohort 1 (20/71, 28%) than in cohort 2 (3/71, 4%) that met the criteria for a possible IFI, (p = .0002, OR = 8.89, 95% CI 2.67–29.2). The number of patients requiring escalation to therapeutic antifungal administration was also significantly higher in cohort 1 (26/71, 37%) than in cohort 2 (9/71, 13%) (p = .001, OR = 3.98, 95% CI 1.71–9.42). In cohort 1, 20 of the 26 patients were escalated to treatment antifungals due to changes in chest computed tomography (CT) scans despite receiving antifungal prophylaxis, while five were escalated secondary to microbiology results. In cohort 2, three of the nine patients were escalated because of chest CT changes while six were escalated based on microbiology results. In cohort 1, the most common drug changes resulting from escalation to treatment therapy were intravenous voriconazole to LAmB on eight occasions, oral posaconazole to LAmB on six occasions, and a change of LAmB from prophylaxis dosing (3 mg/kg three times a week) to treatment dosing (3–5 mg/kg every 24 h) on four occasions. In cohort 2, the most common antifungal switches because of escalation were a change from intravenous/oral posaconazole to LAmB on three occasions and a change from oral posaconazole to anidulafungin on two occasions.

3.3 | Therapeutic drug monitoring

A significantly lower proportion of azole concentrations was within the therapeutic range in cohort 1 (352/521, 68%) compared to cohort 2 (334/428, 78%) (p = .0004, OR = 0.59, 95% CI 0.44–0.79). Azole therapeutic drug monitoring data are presented in Table 3. The proportions of therapeutic posaconazole concentrations during the administration of first line prophylaxis of 142/202 (70%) and 132/192 (69%) for cohorts 1 and 2 respectively was similar (p = .74, OR = 1.08, 95% CI 0.7–1.66). However, in patients who progressed beyond first-line prophylaxis, cohort 1 had a significantly lower rate of therapeutic azole concentrations (210/319, 66%) compared to cohort 2 (202/236, 86%). Overall, in patients who developed proven or probable IFI, 36 of 56 (64%) azole concentrations measured during prophylaxis prior to IFI diagnosis were above the lower limit of the therapeutic range.

3.4 | Cost

Total antifungal drug cost was $359 935 (AUD) more in cohort 1 ($830 486 AUD) compared to cohort 2 ($477 149 AUD), representing a difference of $5069.51 per patient. Drug cost per day of admission was also $85.87 (AUD) more in cohort 1 ($238.20 AUD) than cohort 2 ($154.47 AUD). These differences were due to the decreased use of LAmB in Cohort 2, which offset the increased drug costs of using intravenous posaconazole in the second line.

4 | DISCUSSION

4.1 | Antifungal use

Our study showed that maintaining efficacy and minimizing toxicity without increasing cost of antifungal prophylaxis in alloHCT was achieved with the implementation of a new antifungal prophylaxis pathway.

A difference in the antifungal use profile between the groups was evident following the implementation of the new institutional guidelines. A higher rate of intravenous posaconazole use was seen in cohort 2, replacing intravenous voriconazole and LAmB used in the older algorithm. The successful implementation of the new guideline was likely assisted by the increased simplicity for prescribers, which allowed a change in drug formulation only compared to cohort 1, where a change in both drug and formulation occurred in patients, where the oral administration route was unavailable. The contribution of oral posaconazole use to overall antifungal use was lower in cohort 1, likely due to more patients requiring progression beyond first-line prophylaxis and escalation to antifungal treatment. The significantly higher requirement for greater than one line of antifungal prophylaxis in cohort 1 indicates this group may have had a higher baseline risk of requiring second line prophylaxis. This is an important consideration as first line prophylaxis was the same in both cohorts, thus, this detected a potentially important underlying difference in the groups, which may have confounded some of the results of the study. In cohort 2, the significantly lower number of patients requiring progression beyond second line antifungal prophylaxis represented an advantage of intravenous posaconazole over intravenous voriconazole and was likely because of improved tolerability.

4.2 | Tolerability

A major finding of the study was the significant reduction in drug induced neuropsychiatric toxicity—specifically visual hallucinations in cohort 2, with a reduction of intravenous voriconazole used as prophylaxis. Voriconazole is known to cause neuropsychiatric adverse effects with a reported incidence of between 1% and 37%.[26–28] However, a small study in alloHCT patients did report voriconazole-associated visual disturbances occurring in 70% of patients.[29] The incidence

TABLE 3 Therapeutic drug monitoring—posaconazole and voriconazole (azoles)

	Cohort 1	Cohort 2	Significance (*p*-Value)	Odds ratio/95% confidence interval
Total number of measured azole concentrations (n)	**521**	**428**	-	-
Measured posaconazole concentrations (n)	392	422	-	-
Measured voriconazole concentrations (n)	129	6	-	-
Measured posaconazole concentrations during first-line prophylaxis (n)	202	192	-	-
Measured azole concentrations after first-line prophylaxis (n)	319	236	-	-
No. of azole treatment days per azole concentration measured (n)	**5.3**	**6.0**	**.0004**	**0.59 (0.44–0.79)**
Measured azole concentration within therapeutic range, n (%)	**352 (68)**	**334 (78)**		
Measured posaconazole concentrations within therapeutic range, n (%)	270 (69)	328 (78)	.0054	0.63 (0.46–0.87)
Measured voriconazole concentrations within therapeutic range, n (%)	82 (64)	6 (100)	.092	0 (0–1.3)
Measured posaconazole concentration within therapeutic range during first line prophylaxis, n (%)	142 (70)	132 (69)	.74	1.08 (0.7–1.66)
Measured azole concentrations within therapeutic range after first-line prophylaxis, n (%)	210 (66)	202 (86)	<.0001	0.32 (0.21–0.5)
Measured azole prophylaxis concentration in patients with proven or probable IFI (n)	**12**	**44**	-	-
Measured azole prophylaxis concentrations within therapeutic range in patients with proven or probable IFI, n (%)	**7 (58)**	**29 (66)**	**.1**	**3.19 (0.97–9.72)**

Abbreviation: IFI, invasive fungal infection.

of neuropsychiatric adverse effects in the 48 patients prescribed voriconazole in cohort 1 was 54% ($n = 26$). After assessment using the Naranjo criteria, 19 were deemed to be probably due to voriconazole, representing an incidence of approximately 40%. This is higher than most studies and may indicate that alloHCT patients are more susceptible to this toxicity, and this is likely multifactorial. Increased recognition and reporting of these adverse events may occur in alloHCT patients considering they are often closely monitored hospital inpatients. Other factors include, but are not limited to, polypharmacy and the multiple drug–drug interactions, use of opiate analgesia for acute pain such as mucositis, acute physiological insults and organ dysfunction, acute systemic inflammatory response and psychological factors associated with prolonged admission/illness. We tried to minimize this through therapeutic drug monitoring, as supratherapeutic voriconazole concentrations have been associated with neuropsychiatric adverse effects.[30] However, none of the patients experiencing these events while on voriconazole had a supratherapeutic voriconazole level. The rates of delirium were similar between the groups, and there were some cases of visual hallucinations in cohort 2 in patients not receiving voriconazole. This indicates neuropsychiatric adverse effects likely occur at a baseline rate during the alloHCT procedure.

4.3 | Efficacy

Proven and probable breakthrough IFI occurred at similarly low rates in both groups. However, as with other studies, diagnosing proven or probable IFI is often difficult, and there may be the usual ascertainment bias, although this would have affected our two cohorts equally.[31] Additionally, our study was also not powered to detect a difference in proven or probable breakthrough infections considering these occur at rates of 1%–13% in alloHCT patients on mould-active antifungal prophylaxis.[14,17] There was a greater number of proven infections in cohort 2 compared to cohort 1, and although not statistically significant, due to the small number, this would need to be assessed in a larger cohort to ensure there is no association with a higher risk of IFI. Possible IFIs were significantly higher in cohort 1 compared to cohort 2, although the 2019 EORTC/MSGERC guidelines questioned the clinical usefulness of this category.[22] Significantly more patients also did require escalation to treatment antifungal therapy in cohort 1 compared to cohort 2. However, these differences could be due to confounding factors such as changes in effectiveness of antimicrobial stewardship between the groups and differences in clinicians' thresholds to diagnose a possible IFI and escalate to empiric antifungal treatment. While the difference in most baseline patient characteristics did not reach statistical significance, cohort 1 did have more patients with a previous IFI, more unrelated donors, a higher median age and more frequent use of ATG, all of which are risk factors for IFI in alloHCT patients and may indicate a higher baseline risk in this group.

4.4 | Therapeutic drug monitoring

A lower proportion of measured azole concentrations were within the therapeutic range in cohort 1 due to the significant difference in attainment of target azole concentrations in patients who proceeded beyond first-line antifungal prophylaxis. The change of formulation only in cohort 2 compared to the change of both drug and formulation in cohort 1 when progressing to second-line prophylaxis likely did make it easier to achieve and maintain therapeutic concentra-

tions. Also, the more frequent use of voriconazole in cohort 1 may also explain this. Voriconazole displays greater pharmacokinetic variability than posaconazole, thus it is likely more difficult to achieve voriconazole concentrations within the therapeutic range, and the lack of a loading dose also may have delayed the attainment of target concentrations.

4.5 | Cost

The reduction in the need for treatment with LAmB was the main factor contributing to a reduction in antifungal drug costs in cohort 2. The decreased LAmB use was able to offset the increased cost of using intravenous posaconazole over intravenous voriconazole as second line therapy. The significant reduction in escalation to treatment antifungal therapy is largely responsible for the difference in LAmB usage between the groups. LAmB is currently recommended as the empirical antifungal agent of choice when an IFI is suspected in patients on mould active azole prophylaxis.[13,32,33] Reduction in use of LAmB is beneficial in alloHCT, due to significant rates of nephrotoxicity seen in this patient group. This agent is also responsible for the highest cost burden of the available antifungals.[34] Of note, the increased progression of patients in cohort 1 beyond first line prophylaxis may have contributed to the increased costs in cohort 1 and been a potential confounding factor in this analysis.

4.6 | Study limitations

Considering this was a retrospective observational study, there are important limitations that need to be considered. Confounding factors potentially included changes in clinicians' practice and behaviour over time and some differences in baseline characteristics of patients such as a higher number of myelofibrosis patients in cohort 1 and increased use of the less intense fludarabine 150/busulfan 6.4 conditioning regimen in cohort 2. The study was unblinded, and data collection/review of medical records was only done by a single reviewer, thus reporting and recording of adverse effects may have been susceptible to bias. Inadvertently, cohorts 1 and 2 underwent alloHCT before and during the COVID-19 pandemic respectively, which may have had effects on stem cell donor sources and more delay in proceeding to transplant in cohort 2; however it is unknown how this may have impacted on the study outcomes. We attempted to minimize confounders by analyzing important baseline characteristics of both groups for significant differences. Considering the complexity of alloHCT patients and numerous concomitant therapies and comorbid conditions occurring often simultaneously, analysis of specific issues such as antifungal prophylaxis in this population is difficult. A randomized controlled trial comparing different antifungal prophylaxis strategies utilizing oral and intravenous formulations of different agents first and second line such as posaconazole, itraconazole, and voriconazole in each arm would be the ideal strategy to further determine the best approach to antifungal prophylaxis in the alloHCT setting.

5 | CONCLUSION

This study indicated successful implementation of a new IFI prophylaxis pathway in alloHCT patients, where intravenous posaconazole was the recommended agent in patients unable to tolerate oral antifungal administration. This resulted in reduced actual drug costs and a reduced antifungal adverse effect burden for alloHCT patients in the early posttransplant period.

AUTHOR CONTRIBUTIONS

P. S., S. S., M. W., D. Y., and J. R. conceived the presented idea. Data Collection was done by P. S. All authors were involved in the data analysis. P. S. wrote the first draft of the manuscript, and critical revision was done by all authors. All authors have read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available upon request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Philip R. Selby https://orcid.org/0000-0002-5647-4673

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX 1

Institutional Guideline for Antifungal Prophylaxis in Period 1

- See in separate submitted file (appendices)

APPENDIX 2

Institutional Guideline for Antifungal Prophylaxis in Period 2

- See in separate submitted file (appendices)