Received: 5 November 2021 | Revised: 15 December 2021 | Accepted: 17 December 2021

DOI: 10.1111/myc.13416

ORIGINAL ARTICLE

mycoses Diagnosis, Therapy and Prophylaxis of Fungal Diseases WILEY

Frequency and causes of antifungal treatment changes in allogeneic haematopoïetic cell transplant recipients with invasive mould infections

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Funding information
This study was, in part, supported by a research grant from Pfizer (59276319 – WP2485056)

Abstract

Background: Antifungal treatment duration and changes for invasive mould infections (IMI) have been poorly described.

Methods: We performed a 10-year cohort study of adult (≥18-year-old) allogeneic haematopoietic cell transplant recipients with proven/probable IMI to describe the duration and changes of antifungal treatment. All-cause-12-week mortality was described.

Results: Sixty-one patients with 66 IMI were identified. Overall treatment duration was 157 days (IQR: 14–675) and 213 (IQR: 90–675) days for patients still alive by Day 84 post-IMI diagnosis. There was at least one treatment change in 57/66 (86.4%) cases: median 2, (IQR: 0–6, range:0–8). There were 179 antifungal treatment changes due to 193 reasons: clinical efficacy (104/193, 53.9%), toxicity (55/193, 28.5%), toxicity or drug interactions resolution (15/193, 7.8%) and logistical reasons (11/193, 5.7%) and 15/193 (7.8%) changes due to unknown reasons. Clinical efficacy reasons included lack of improvement (34/104, 32.7%), targeted treatment (30/104, 28.8%), subtherapeutic drug levels (14/104, 13.5%) and other (26/104, 25%). Toxicity reasons included hepatotoxicity, nephrotoxicity, drug interactions, neurotoxicity and other in 24 (43.6%), 12 (21.8%), 12 (21.8%), 4 (7.4%) and 3 (5.5%) cases respectively. All-cause 12-week mortality was 31% (19/61), higher in patients whose antifungal treatment (logrank 0.04) or appropriate antifungal treatment (logrank 0.01) was started >7 days post-IMI diagnosis. All-cause 1-year mortality was higher in patients with ≥2 changes of treatment during the first 6 weeks post-IMI diagnosis (logrank 0.008) with an OR: 4.00 ($p = .04$).

Conclusions: Patients with IMI require long treatment courses with multiple changes for variable reasons and potential effects on clinical outcomes, demonstrating the

This study was, in part, presented as an oral poster (P244) at the 10th Trends in Medical Mycology, TIMM, Aberdeen, UK, October 8-11, 2011.

need more effective and safer treatment options. Early initiation of appropriate antifungal treatment is associated with improved outcomes.

KEYWORDS
allogeneic haematopoietic cell transplant recipients, antifungal treatment changes, invasive aspergillosis, invasive mould infections, mortality, surgical treatment

1 | INTRODUCTION

Despite significant progress in their management during the last several decades, invasive mould infections (IMI) remain a common complication in allogeneic haematopoietic cell transplant (HCT) recipients, frequently associated with poor clinical outcomes.[1–4] Notably, 12-week mortality of allogeneic HCT recipients with invasive aspergillosis (IA) appears to have remained relatively stable in the range of 25%–30% since the early 2000s.[1–3,5–11] Host factors, considering that allogeneic HCT recipients in the recent years have more comorbidities and remain profoundly immunosuppressed for longer when compared to prior, may be important contributors to those stagnating survival rates. However, gaps and inadequacies in current treatment options may also contribute to lack of more favourable outcomes.[11] Administration of antifungal agents is frequently modified for variable reasons, including renal or liver dysfunction, ability to receive and absorb orally (PO) administered agents, potential drug interactions, and associated costs.[12–16] This is pertinent, particularly when considering the long duration of antifungal treatment for an IMI, almost unanimously longer than the traditional 12 weeks of treatment administered in the setting of clinical trials. We hypothesised that allogeneic HCT recipients with IMI require multiple treatment changes during their long treatment courses with a potential effect on clinical outcomes. We performed a retrospective cohort study, to describe the treatment of proven and probable IMI in a large cohort of allogeneic HCT recipients, including agent selection and changes, treatment duration and potential effects on all-cause mortality.

2 | METHODS

2.1 | Study design

This was a retrospective observational single-centre cohort study performed from 1 January 2010 through 1 January 2020. During the study period, 515 allogeneic HCT were performed. All adult (≥18-year-old) allogeneic HCT recipients who were treated for a proven or probable IMI during the study period were included. The study was approved by the institutional Ethics Committee (2020-01072). Allogeneic HCT recipients were identified through the institutional HCT-database and pertinent HCT and IMI data were collected, as previously described.[11]

2.2 | Data collection

The following variables were collected through the HCT-database: (1) demographics : age, gender, (2) HCT-related variables: underlying malignancy leading to HCT, conditioning regimen (myeloablative, reduced intensity), HCT-donor type (matched related, matched/mismatched unrelated, or haplo-identical donor), HCT source (bone marrow, peripheral blood stem cells), GvHD prophylaxis regimen, and the cytomegalovirus (CMV) serostatus of donors (D) and recipients (R), (3) post-HCT complications: ≥grade 2 acute and chronic GvHD, disease relapse, and graft loss. A detailed review of all patient charts was performed to identify patients with proven and probable IMI, as previously described.[11] For all patients with a proven and probable IMI, detailed data on antifungal treatment were collected, including the following variables: the reasons that prompted the selection of primary empirical antifungal treatment, the number of changes in antifungal agents during the treatment course, the reasons that prompted those changes, the duration of antifungal treatment and the reasons that prompted the decision to discontinue them—including treatment completion, death and loss to follow-up. Information about potential surgical interventions for the management of IMI was also collected.

2.3 | Study objectives

We hypothesised that antifungal treatment administration requires multiple changes during a full treatment course. The primary objective of this study was to describe the duration of antifungal treatment and the number and reasons of antifungal treatment changes for an IMI in allogeneic HCT recipients. Treatment changes were divided in three major categories: clinical efficacy, toxicity and logistical reasons. Clinical efficacy reasons prompting a treatment change included clinical improvement, clinical deterioration, clinical suspicion of IA or non-IA IMI, targeted treatment or subtherapeutic TDM for azoles, as assessed by the treating physicians. Toxicity included liver or renal function impairment, neurotoxicity or drug interactions, as assessed by the clinical team caring for those patients. Logistical reasons included changes due to insurance coverage or to facilitate patient discharge, such as when changing intravenously (IV) administered to PO treatment. As secondary objectives we sought to describe the: (1) time to initial and appropriate antifungal treatment after IMI diagnosis, time to treatment discontinuation

and time to treatment first change, and (2) all-cause mortality by 12-week after IMI diagnosis and the effect of treatment changes on overall survival.

2.4 | Definitions

Proven and probable IMI were defined based on revised consensus guidelines.[17] Day of IMI diagnosis was defined as the day on which the first diagnostic test was obtained. Pre-HCT IMI were defined as all proven or probable IMI that were diagnosed during the administration of induction chemotherapy for acute myelogenous leukaemia (AML) and prior to an allogeneic HCT. Mould-active azoles included voriconazole, posaconazole and isavuconazole, echinocandins included caspofungin and anidulafungin, and lipid formulations amphotericin-B included liposomal-amphotericin-B. Initial antifungal treatment was the first antifungal agent used upon clinical suspicion of IMI. Appropriate antifungal treatment was defined based on available antibiogram, literature evidence on mould-susceptibility to antifungal agents in cases without available susceptibility data, and international consensus guidelines.[5,7,8,18–22] Briefly, appropriate treatment for IA included any of the three mould-active azoles and/or liposomal-amphotericin-B (except for the treatment of *A terreus* infections for the latter).[5,7,8,18,19,21] Monotherapy with an echinocandin was not considered appropriate treatment for IA, although endorsed as second-line treatment by international guidelines.[19,21] Treatment for mucormycosis was considered appropriate if posaconazole, isavuconazole or liposomal-amphotericin-B was administered.[20,22] For non-*Aspergillus*, non-*Mucorales* IMI appropriate treatment was defined on a case-by-case basis considering all available microbiology and literature data. Time to initial treatment administration was defined as the time from IMI diagnosis to the first day of antifungal treatment administration. Time to appropriate treatment initiation was defined as the time from IMI diagnosis to the first day appropriate antifungal treatment was administered. Targeted treatment was defined as antifungal treatment administered based on the type of microbiologically confirmed or biopsy-proven IMI. Combination treatment was defined as the concomitant administration of more than one agents from different antifungal classes for ≥3 consecutive days. A treatment course was defined as the administration of any antifungal therapy (either as monotherapy or combination therapy) from the time it was administered until it was changed or stopped.

2.5 | Statistical analysis

Continuous variables were described as median with interquartile range (IQR). Categorical and continuous variables were compared with the Fisher's exact and a two-tailed Student's *t*-test respectively. Risk factor analysis to identify predictors of mortality were performed with logistic regression. Independent variables with $p < .10$ in the univariable analyses were subsequently entered in a backward stepwise fashion into multivariable logistic regression models with mixed effect. Results are presented as odds ratios (OR) with 95% confidence intervals (CI). The Pearson correlation coefficient was used to determine the strength of possible correlations between independent variables. The overall 12-week and 1-year all-cause mortality were analysed using Kaplan-Meier survival curves. The logrank test was used to compare survival distribution between groups. A two-sided test was performed, and a $p < .05$ was considered to be statistically significant. For patients with more than one IMI diagnosis, the most recent IMI was considered for mortality analysis. Data were analysed using STATA 16.0 (StataCorp).

TABLE 1 Characteristics of 61 allogeneic haematopoietic cell transplant recipients who received antifungal treatment for 66 proven/probable invasive mould infections

Characteristics	Patients *N*: 61 (%)
Demographics	
Age, Median years (IQR)	56 (26, 7)
Gender, Male	39 (63.9)
HCT-related variables	
Conditioning, Reduced intensity	47 (77.1)
HCT source, Peripheral blood stem cells	49 (80.3)
Donor	
Matched related	15 (24.6)
Matched unrelated	27 (44.3)
Haplo-identical	14 (23.0)
Mismatched unrelated	5 (8.2)
Acute GvHD ≥grade 2	37 (60.7)
Chronic GvHD	14 (23.0)

Abbreviations: GvHD: graft-versus-host disease; HCT, haematopoietic cell transplant; IQR, interquartile range; *N*, number.

3 | RESULTS

3.1 | Patient population

There were 61 patients with 66 proven/probable IMI identified: 47/66 (71%) IA, 11/66 (17%) mucormycosis and 8/66 (12%) other IMI, including 3 *Fusarium* spp., and 1 each: *Alternaria* spp., *Hormographiella aspergillata*, *Scedosporium* spp., *Schizophyllum commune and Scopulariopsis* spp. More than two-thirds (43/61, 70%) of patients had their IMI diagnosed post-HCT, while 14/61 (23%) had an IMI pre-HCT and 4/61 (7%) had an IMI both pre- and post-HCT. The median age was 56-year-old (IQR: 26, 69), and the majority of patients were male (39, 64%; Table 1).

3.2 | Antifungal treatment initiation

Antifungal treatment initiation was observed at a median time of 1 (IQR: 0, 8) day post-IMI diagnosis (Figure 1A): 0 (IQR: 0, 7) days for

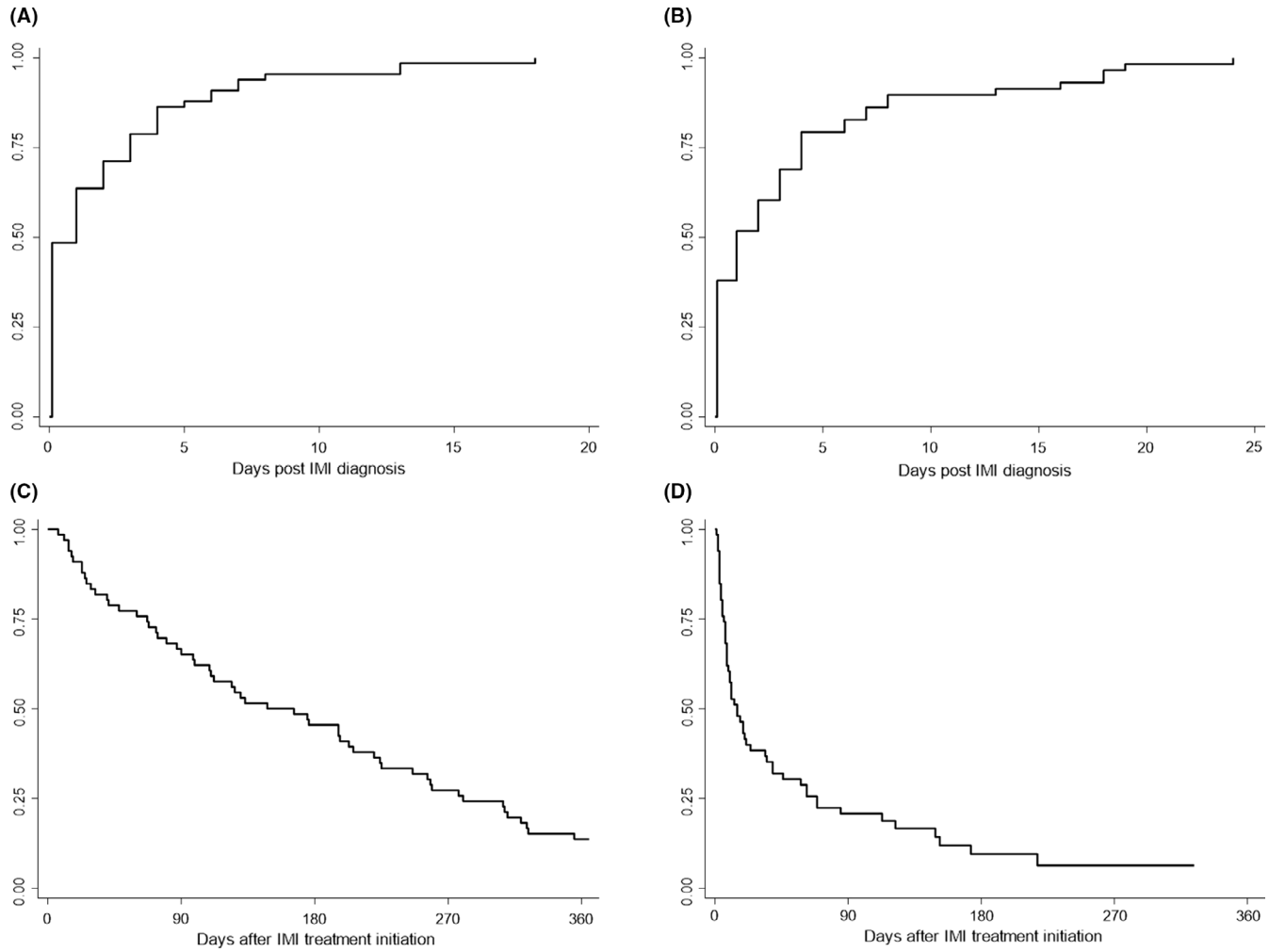


FIGURE 1 Kaplan-Meier curves showing: (A) time to treatment initiation (Day 0 is the day of IMI diagnosis), (B) time to initiation of appropriate treatment (Day 0 is the day of IMI diagnosis), (C) time to first change of administered treatment (Day 0 represents the first day of antifungal treatment administration) and (D) time to treatment discontinuation (Day 0 represents the first day of antifungal treatment administration

IA and 1 (IQR: 0, 18) day for non-IA IMI ($p = .30$). Appropriate antifungal treatment was administered at a median of 1 (IQR: 0, 18) day post-IMI diagnosis (Figure 1B): 0 (IQR: 0, 7) days for IA and 3 (IQR: 0, 24) days for non-IA IMI ($p = .001$). Monotherapy only was used for the treatment of 31 (47%) IMI, followed by alternating monotherapy and combination therapy in another 31 (47%) IMI, while in 4 (6%) cases only combination treatment was administered. A mould-active azole was the most frequently administered first-line treatment (38, 48.7%), followed by liposomal amphotericin-B (29 (37.2%) and echinocandins (11, 14.1%). Initial treatment selection was predominately based on clinical efficacy reasons (61, 92.4%).

3.3 | Antifungal treatment duration

Median time to treatment discontinuation was 157 (IQR: 14, 675) days (Figure 1C): 175 (IQR: 14, 577) and 124 (IQR: 14, 809) for IA and non-IA IMI respectively ($p = .90$). Treatment was completed in 19 (27.3%) cases and was prematurely discontinued due to death or palliative care in more than half of cases (40, 60.6%). For patients still alive by 12 weeks post-IMI diagnosis, median time to treatment discontinuation was 213 (IQR: 90, 675) days: 200 (IQR: 87, 577) and 293.5 (IQR: 99, 809) for IA and non-IA IMI respectively ($p = .07$). A surgical intervention for the treatment of IMI was performed in 14 (21%) cases: 7 (15%) and 7 (37%) cases of IA and non-IA IMI respectively ($p = .09$).

3.4 | Changes of antifungal treatment

There were no changes of antifungal treatment performed in 9 (13.6%) IMI, while at least one change in antifungal treatment was observed in the remaining 57 (86.4%) IMI (Table 2). The first change of antifungal treatment was observed at a median of 11 (IQR: 2, 152) days post-treatment initiation (Figure 1D): 9.5 (IQR: 2.5, 162.5) and 15 (IQR: 2, 149) for IA and non-IA IMI respectively ($p = .88$). The

TABLE 2 Description of antifungal treatment for 66 proven or probable invasive mould infections

	IMI *N*: 66 (%)	IA* *N*: 47 (%)	Non-IA IMI* *N*: 19 (%)	Mucormycosis *N*: 11 (%)	Other IMI *N*: 8 (%)	*p**
Certitude of IMI diagnosis, Proven	17 (25.8)	8 (17.0)	9 (47.4)	8 (72.7)	1 (12.5)	.03
IMI diagnosis timing—Number of pre-HCT IMI diagnosis	18 (27.3)	14 (29.8)	4 (21.1)	2 (18.2)	2 (25.0)	1.00
Treatment initiation, Median days (IQR)[1]	1 (0, 8)	0 (0, 7)	1 (0, 18)	2 (0, 18)	0.5 (0, 3)	.30
Appropriate treatment initiation, Median days (IQR)[1,2]	1 (0, 18)	0 (0, 7)	3 (0, 24)	4 (2, 18)	1 (0, 24)	.001
Treatment change, median number (IQR)	2 (0, 6)	2 (0, 6)	2 (0, 8)	2 (1, 8)	3 (0, 6)	.88
No treatment changes	9 (13.7)	7 (14.9)	2 (10.5)	0 (0.0)	2 (25.0)	
Only one treatment change	35 (53.0)	24 (51.1)	11 (57.9)	9 (81.8)	2 (25.0)	
≥2 treatment changes	22 (33.3)	16 (34.0)	6 (31.6)	2 (18.2)	4 (50.0)	
Type of treatment						.43
Monotherapy only	31 (47.0)	24 (51.0)	7 (36.9)	3 (23.3)	4 (50.0)	
Combination therapy only	4 (6.0)	2 (4.3)	2 (10.5)	2 (18.2)	0 (0.0)	
Monotherapy and combination therapy	31 (47.0)	21 (44.7)	10 (52.6)	6 (54.5)	4 (50.0)	
Initial antifungal agent administered[3]						.15
Mould-active azole	38 (48.7)	27 (50.0)	11 (45.8)	8 (53.4)	3 (33.3)	
Voriconazole	27 (34.6)	22 (40.7)	5 (20.8)	4 (26.7)	1 (11.1)	
Posaconazole	10 (12.8)	4 (7.4)	6 (25.0)	4 (26.7)	2 (22.2)	
Isavuconazole	1 (1.3)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	
L-AMB	29 (37.2)	20 (37.0)	9 (37.5)	5 (33.3)	4 (44.5)	
Echinocandin[4]	11 (14.1)	7 (13.0)	4 (16.7)	2 (13.3)	2 (22.2)	
Reason for 1st antifungal treatment selection[5]						
Clinical efficacy	61 (92.4)	44 (93.6)	17 (89.5)	9 (81.8)	8 (100)	1.00
Toxicity [6]	4 (6.1)	4 (8.5)	0 (0.0)	0 (0.0)	0 (0.0)	.32
Logistical [7]	1 (1.5)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1.00
Treatment duration						
Overall, Median (IQR)	157 (14, 675)	175 (14, 577)	124 (14, 809)	280 (25, 809)	116.5 (14, 310)	.90
For patients alive by Day 84, Median (IQR)	213 (90, 675)	200 (87, 577)	293.5 (99, 809)	491.5 (280, 809)	145 (99, 310)	.07
Diagnosis pre-HCT, Median (IQR)	277 (16, 2016)	268 (16, 2016)	492.5 (109, 740)	707.5 (675, 740)	209.5 (109, 310)	.80
Diagnosis post-HCT, Median (IQR)	112 (14, 470)	112 (11, 470)	99 (14, 809)	80 (25, 809)	111.5 (14, 220)	.68
Surgical intervention	14 (21%)	7 (15%)	7 (24%)	5 (46%)	2 (25%)	.09
Treatment stop reason						
Treatment completion	19 (27.3)	14 (29.8)	5 (26.3)	3 (27.3)	2 (25.0)	1.00
Death	26 (39.4)	18 (38.3)	8 (42.1)	5 (45.5)	3 (37.5)	.79
Palliative care	14 (21.2)	11 (23.4)	3 (15.8)	1 (9.1)	2 (25.0)	.74
Loss to follow-up	5 (7.6)	3 (6.4)	2 (10.5)	1 (9.1)	1 (12.5)	.62
Other [8]	2 (3.0)	1 (2.1)	1 (5.3)	1 (9.1)	0 (0.0)	.50

Abbreviations: GvHD, graft-versus-host disease; HCT, haematopoietic cell transplant; IA, invasive aspergillosis; IMI, invasive mould infection; IQR, interquartile range; L-AMB, liposomal amphotericin-B; *N*, number; *p*, *p*-value.

[1]Median days after the diagnosis of an IMI.

[2]Appropriate treatment was defined based on available antibiogram, literature evidence on mould-susceptibility to antifungal agents in cases without available susceptibility data, and international consensus guidelines, as described in the manuscript Methods.[2-9]

[3]A total of 78 agents were used as initial antifungal treatment for 66 proven/probable IMI: 55 of 66 cases were treated with one agent only and 11 of 66 cases received combination antifungal treatment with 2 agents[10] and 3 agents.[1]

[4]Echinocandin treatment was administrated as first-line treatment in 11 cases, including 7 cases as combination therapy. Echinocandin selection was motivated by clinical efficacy, toxicity and logistical reasons in 8, 2 and 1 cases respectively.

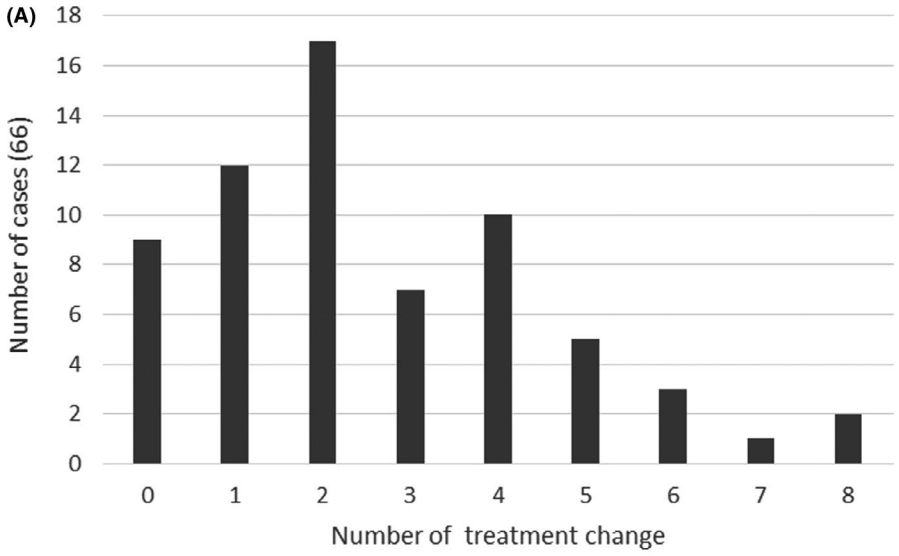
[5]Two cases had >1 reason for their antifungal treatment selection (clinical efficacy and toxicity). In 2 cases, there was no documented reason for the selection of antifungal treatment.

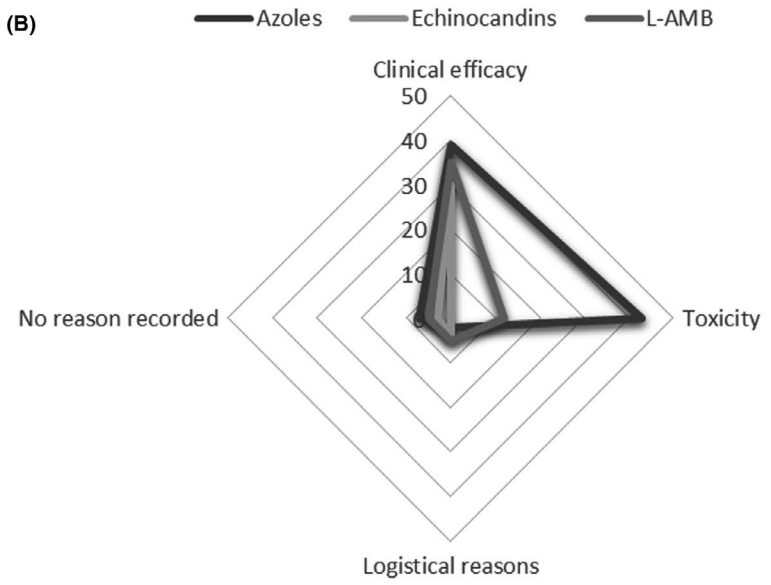
[6]Four patients had their first treatment selection due to toxicity reasons: liver toxicity,[1] gastrointestinal toxicity[1] and potential drug interactions.[2]

[7]One patient had their first treatment selection due to lack of intravenous voriconazole stock.

[8]Other included 2 patients, who had their treatment stopped because of a new IMI diagnosis.

**p* represents the *p*-value comparing patients with IA vs non-IA IMI.





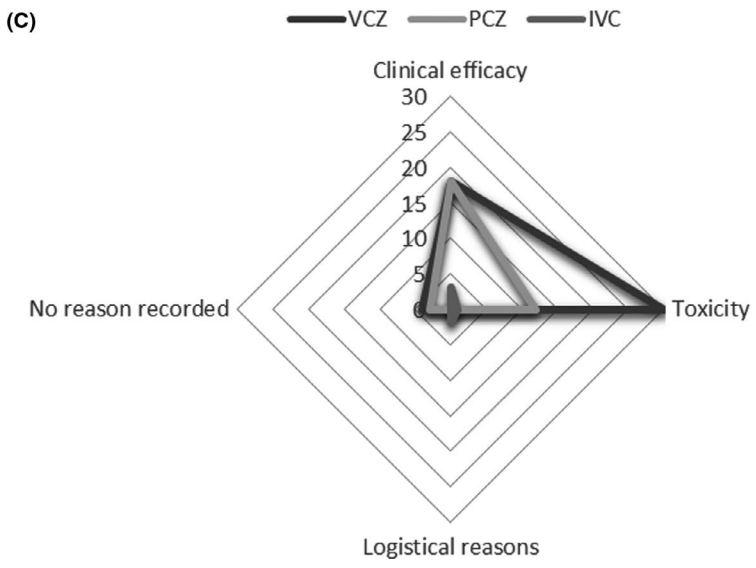


FIGURE 2 (A) Presentation of number of changes of antifungal treatment for the 66 probable or proven invasive mould infection (IMI) of our study. (B) Distribution of antifungal treatment changes. Each line on the dial represents an absolute number of 10 changes recorded for clinical efficacy, toxicity or logistical reasons - clockwise. (C) Distribution of antifungal treatment changes in patients treated with an azole. Each line on the dial represents an absolute number of 5 changes recorded

median number of changes was 2 (IQR: 0, 6), with a range of 0 to 8 changes overall (Figure 2A): 2 (IQR: 0, 6) and 2 (IQR: 0, 8) in patients with IA and non-IA IMI respectively ($p = .88$).

There were 240 treatment courses for the treatment of 66 IMI administered during the study period: 178 and 62 courses of monotherapy and combination therapy respectively. Excluding 61 of 240 treatment courses stopped due to treatment completion or loss to follow-up, treatment changes were recorded for the remaining 179 treatment courses. Considering that one treatment change could have been prompted by >1 reasons, 193 reasons led to 179 antifungal agent changes, as detailed in Table 3. Treatment changes were prompted by clinical efficacy (97/193, 50%), toxicity (70/193, 36%) and logistical reasons (11/193, 6%); in 15 (8%) changes, there were no reasons documented in the patient chart (Figure 2B,C). Clinical efficacy reasons included treatment escalation due to lack of clinical improvement (35%), targeted treatment (24%), subtherapeutic therapeutic drug monitoring (TDM, 15%), clinical suspicion for IA (12%), treatment de-escalation for clinical improvement (8%) and clinical suspicion for non-IA IMI (6%; Figure S1A). Toxicity reasons leading to treatment changes included hepatotoxicity (44%), nephrotoxicity (22%), drug interactions (22%), neurotoxicity (7%) and other reasons (5%;

TABLE 3 Detailed description of 193 reasons leading to 179 antifungal agent changes during the treatment of 66 proven/probable invasive mould infections

	Overall *N*: 179	Azoles *N*: 85 (%)	Echinocandins *N*: 41 (%)	L-AMB *N*: 53 (%)	*p**	VCZ *N*: 48 (%)	PCZ *N*: 32 (%)	IVC *N*: 5 (%)
Treatment change reasons[1]	193 (%)	91 (%)	44 (%)	58 (%)		52 (%)	33 (%)	6 (%)
Clinical efficacy	97 (50.2)	39 (42.8)	23 (52.3)	35 (60.4)	.07	18 (34.6)	18 (54.5)	3 (50.0)
Lack of clinical improvement	34 (35.1)	18 (46.1)	6 (26.1)	10 (28.6)	.84	9 (50.0)	8 (44.4)	1 (33.3)
Targeted treatment	23 (23.7)	6 (15.4)	8 (34.8)	9 (25.7)	.07	2 (11.1)	3 (16.7)	1 (33.3)
Subtherapeutic TDM[2]	14 (14.4)	12 (30.8)	1 (4.4)	1 (2.8)	.01	5 (27.7)	7 (38.9)	0 (0.0)
Clinical suspicion for IA	12 (12.4)	0 (0.0)	3 (13.0)	9 (25.7)	.001	0 (0.0)	0 (0.0)	0 (0.0)
Clinical improvement	8 (8.2)	2 (5.1)	3 (13.0)	3 (8.6)	.62	1 (5.6)	0 (0.0)	1 (33.3)
Clinical suspicion for non-IA IMI	6 (6.2)	1 (2.6)	2 (8.7)	3 (8.6)	.62	1 (5.6)	0 (0.0)	0 (0.0)
Toxicity	55 (28.5)	43 (47.3)	0 (0.0)	12 (20.7)	<.001	30 (57.7)	12 (36.4)	1 (16.7)
Hepatotoxicity	24 (43.6)	23 (53.4)	0 (0.0)	1 (8.3)	<.001	15 (50.0)	8 (66.6)	0 (0.0)
Nephrotoxicity	12 (21.8)	2 (4.7)	0 (0.0)	10 (83.4)	.001	2 (6.7)	0 (0.0)	0 (0.0)
Drug interactions [3]	12 (21.8)	12 (27.9)	0 (0.0)	0 (0.0)	.001	9 (30.0)	2 (16.7)	1 (100)
Neurotoxicity	4 (7.3)	3 (7.0)	0 (0.0)	1 (8.3)	.81	3 (10.0)	0 (0.0)	0 (0.0)
Other [4]	3 (5.5)	3 (7.0)	0 (0.0)	0 (0.0)	.32	1 (3.3)	2 (16.7)	0 (0.0)
Toxicity and drug interactions resolution [5]	15 (7.8)	0 (0.0)	14 (31.8)	1 (1.7)	<.001	0 (0.0)	0 (0.0)	0 (0.0)
Logistical reasons	11 (5.7)	2 (2.2)	4 (9.1)	5 (8.6)	.10	0 (0.0)	0 (0.0)	2 (33.3)
IV to PO	8 (72.7)	0 (0.0)	3 (75.0)	5 (100)	.007	0 (0.0)	0 (0.0)	0 (0.0)
Insurance coverage	3 (27.3)	2 (100)	1 (25.0)	0 (0.0)	.60	0 (0.0)	0 (0.0)	2 (100)
No reason recorded[1]	15 (7.8)	7 (7.7)	3 (6.8)	5 (8.6)	1.00	4 (7.7)	3 (9.1)	0 (0.0)

Abbreviations: GIT, gastrointestinal tract; IA, invasive aspergillosis; IMI, invasive mould infection; IV, intravenous; IVC, isavuconazole; L-AMB, liposomal amphotericin-B; *N*, number; *p*, *p*-value; PCZ, posaconazole; PO, oral; TDM, therapeutic drug monitoring; VCZ, voriconazole.

[1]A treatment change refers to discontinuation of prior administered treatment and could have been prompted by more than one reasons. For 15 treatment changes in 6 patients there were no reasons documented in the patients' charts. In case of combination therapy, changes were recorded per agent and not per treatment course.

[2]In 2 cases, an echinocandin[1] and liposomal amphotericin-B[1] were administrated until therapeutic blood concentrations of azoles were obtained.

[3]There were 12 cases in which an azole was changed due to potential drug interactions with conditioning regimen[7] and due to co-administration with other agents,[5] including anti-tuberculosis, amikacin, aprepitant, posaconazole and sirolimus, one each.

[4]In 2 cases, a treatment of posaconazole was discontinued because of suspected fever associated with this treatment[1] and QTc prolongation.[1] Voriconazole treatment was discontinued in one case because of a skin reaction.

[5]In 8 cases, liposomal amphotericin-B[1] and echinocandin[7] were used to replace an azole due to azole-associated liver toxicity and were eventually discontinued and replaced by another treatment upon resolution of liver test abnormality. In 7 cases, an echinocandin was prescribed instead of an azole, in order to avoid drug interactions between an azole with conditioning regimen (5 cases), sirolimus (1 case) and ongoing anti-tuberculosis treatment (1 case) and were discontinued once those treatments were stopped.

*p represents the p-value comparing azoles, echinocandins and liposomal amphotericin-B.

Figure S1B). Azoles were the most commonly changed agents due to drug toxicity (47% vs. 21% and 0% for L-AMB and echinocandins, respectively, $p < .001$), mainly due to hepatotoxicity (53% vs. 8% and 0% for liposomal amphotericin-B and echinocandins, respectively, $p < .001$) and drug interactions (28% vs. 0% and 0% for liposomal amphotericin-B and echinocandins, respectively, $p = .001$). Nephrotoxicity was predominately associated with the administration of liposomal amphotericin-B (77% vs. 5% and 0% for azoles and echinocandins, respectively, $p = .001$). Notably, echinocandins and amphotericin-B were administered as a 'bridge' in 15 cases, to either avoid drug interactions and/or azole-associated toxicities, as detailed in Table 2. Considering that this indication was not a direct drug-associated toxicity, those cases were summarised under a different title: 'Toxicity and drug interaction resolution'. Logistical reasons included the need to change from IV to PO administered antifungal therapy (73%) and insurance coverage issues (27%), with echinocandins (9.1%) being the most commonly involved agents, followed by liposomal amphotericin-B (8.6%) and azoles (2.2%, $p = .10$).

3.5 | Mortality

All-cause 12-week mortality after a diagnosis of IMI was 31% (19/61): 30% (13/43) and 33% (6/18) for patients with IA and non-IA IMI respectively (logrank 0.82). All-cause 12-week mortality was higher in patients, whose antifungal treatment (logrank 0.04; Figure 3A) or appropriate antifungal treatment (logrank 0.01; Figure 3B) was started >7 days post-IMI diagnosis respectively. When considering only patients, who remained alive during the first 6 weeks post-IMI diagnosis, there was a trend for higher 12-week mortality in patients with ≥2 versus 0-1 changes of antifungal treatment performed during the first 6 weeks post-IMI (logrank 0.15; Figure 3C). A surgical intervention for the management of IMI was associated with improved 12-week survival (logrank 0.008; Figure 3D). The latter was more evident in patients with non-IA IMI, when compared to patients with IA (Figure S2A,B). Logistic regression (Table 4) identified earlier initiation of appropriate antifungal treatment (0-7 vs. >7 days) as a significant predictor of 12-week survival post-IMI (OR: 5.86, 95% CI 1.1, 30.7, $p = .04$).

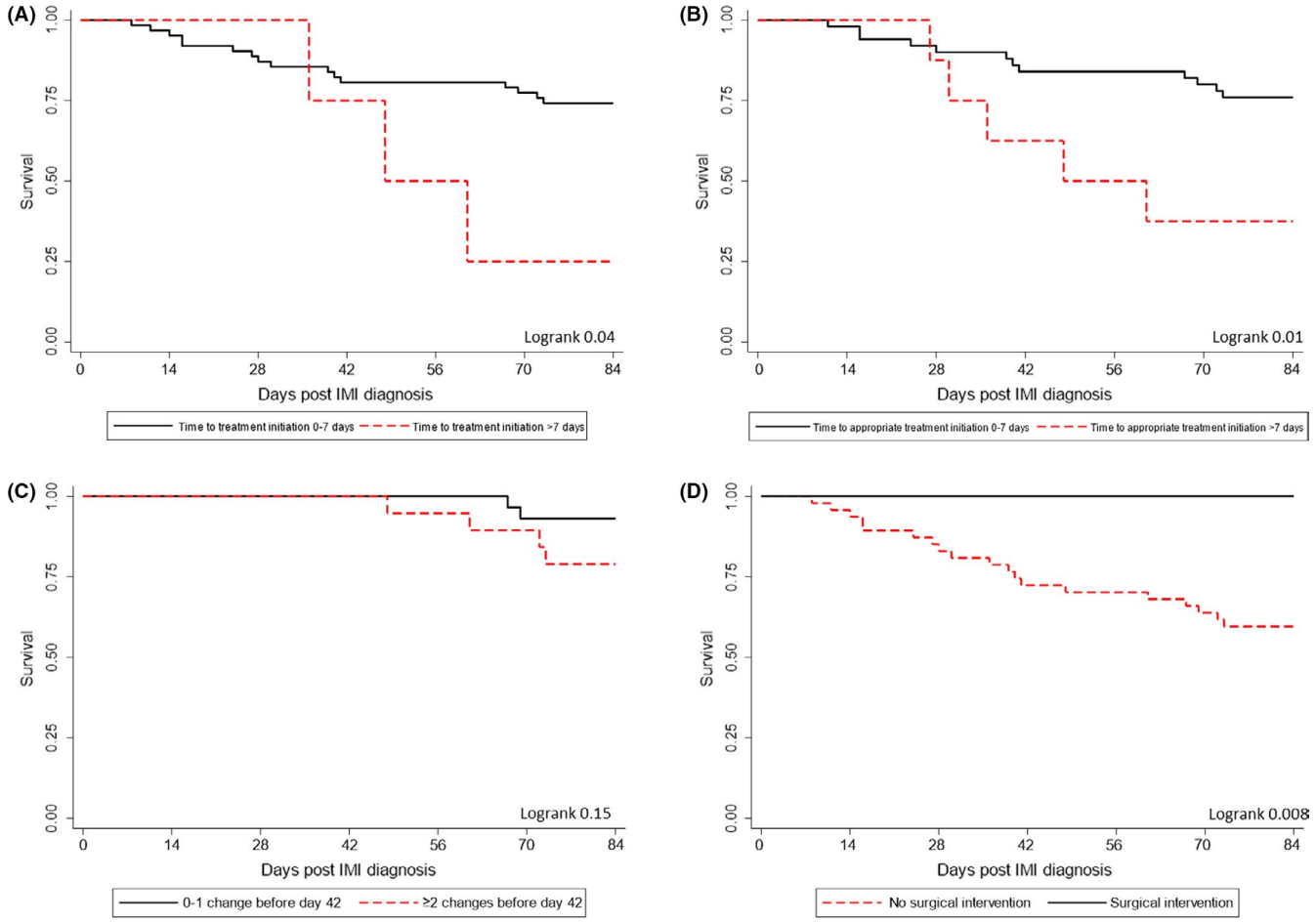


FIGURE 3 All-cause 12-week mortality for 61 patients with proven or probable invasive mould infections (IMI) based on: (A) time to antifungal treatment initiation: 0–7 days versus >7 days post-IMI diagnosis, (B) time to appropriate antifungal treatment initiation: 0–7 days versus >7 days post-IMI diagnosis, (C) number of changes of antifungal treatment during the first 42 days post-IMI: 0–1 versus ≥2 changes; only patients alive until Day 42 post-IMI diagnosis were included for these analyses, and (D) surgical intervention versus not for the management of IMI

TABLE 4 Risk factor analysis to identify predictors of all-cause 12-week and 1-year mortality after a diagnosis of a proven or probable invasive mould infection

	Univariable analyses			Multivariable analyses[1]		
	OR	95% CI	*p*	OR	95% CI	*p*
12-week mortality predictors						
Certainty of IMI diagnosis, Probable vs Proven	0.26	0.05, 1.4	.10	0.26	0.05, 1.4	.12
Type of IMI, IA vs. non-IA IMI	0.87	0.27, 2.8	.81			
Days to treatment initiation, 0–7 vs. >7	7.69	0.7, 79.5	.09*			
Days to appropriate treatment initiation, 0–7 vs. >7	5.28	1.1, 25.4	.04	5.86	1.1, 30.7	.04
Treatment change before Day 42, 0-1 vs. ≥2	1.62	0.5, 4.9	.39			
Surgical intervention, Yes vs. No	NA					
1-year mortality predictors						
Certainty of IMI diagnosis, Probable vs Proven	0.20	0.06, 0.69	.01	0.45	0.08, 2.56	.37
Type of IMI, IA vs non-IA IMI	1.07	0.3, 3.3	.90			
Days to treatment initiation, 0–7 vs. >7	1.89	0.18, 19.3	.59			
Days to appropriate treatment initiation, 0–7 vs. >7	5.07	0.6, 44.4	.14			
Treatment change before Day 42, 0–1 vs. ≥2	3.6	1.1, 11.7	.03	4.00	1.01, 15.0	.04
Surgical intervention, Yes vs. No	0.24	0.07, 0.83	.02	0.31	0.05, 2.03	.22

Abbreviations: CI, confidence interval; IA, invasive aspergillosis; IMI, invasive mould infection; NA, not applicable; OR, odds ratio; *p*, *p*-value.

[1]Only variables with a $p \leq .10$ in univariable analyses were introduced into the logistic regression model in a stepwise backwards fashion.

*A strong interaction was detected between time to treatment initiation and appropriate treatment initiation (Pearson correlation coefficient: 0.68, $p < .0001$); hence, the variable days to treatment initiation was not considered in multivariable analyses.

To further study the potential effect of treatment changes on overall survival, we calculated 1-year survival among those patients that were alive during the first 6 weeks post-IMI diagnosis. All-cause 1-year mortality was significantly higher in patients who had ≥2 versus 0–1 changes of antifungal treatment performed during the first 6 weeks post-IMI (logrank 0.008; Figure S3). Logistic regression (Table 4) demonstrated that ≥2 treatment changes during the first 6 weeks of antifungal treatment were the only predictor of 1-year mortality (OR: 4.00, 95% CI 1.01, 15.0, $p = .04$).

4 | DISCUSSION

This single-centre retrospective cohort study provides important information on the treatment of IMI in allogeneic HCT recipients, showing long treatment courses requiring multiple changes, prompted by a large variety of reasons. In contrast to current guidelines recommending a predefined duration of 12 weeks for the treatment of IA and up to 3–6 months for mucormycosis, our data suggest that antifungal treatment for IMI in high-risk haematology patients is administered for much longer.[19–21] When focusing on patients still alive by 12 weeks, treatment duration was at an average of 30 weeks: 28 for IA and 1.3 years for mucormycosis. It is likely that in a number of patients antifungal treatment could have been continued as secondary prophylaxis in the setting of continuous high-grade immunosuppression. The latter could explain, in part, the long treatment courses reported in this study. However, considering the retrospective nature of this study over a decade, differentiating between primary antifungal treatment and secondary prophylaxis through chart review was not feasible. Regardless, these findings underscore an important gap between clinical trials and real life in the management of IMI. Clinicians may consider multiple factors when treating high-risk patients for an IMI prior to deciding when to discontinue antifungal treatment. In addition to clinical and radiographical resolution of the infection, the patient net degree of immunosuppression remains an important determining factor.[19–21,23] Factors, such as treatment of refractory/chronic GvHD, administration of post-HCT chemotherapy to prevent disease relapse, administration of donor lymphocyte infusions, disease relapse and retransplantation, may further impact clinical decision-making at the bedside. It is likely that clinicians may opt for longer treatment courses in patients, whose infection may seem resolved, but whose immune status remains fragile. This was even more evident in patients with mucormycosis in our study, treated on average for more than a year. Our data show that the risk for high mortality associated with this infection

may lead clinicians to recommend prolonged treatment courses for the treatment of mucormycosis.

In this study, we sought to explore and describe in a concise and consistent manner all changes made during the treatment course of IMI. Eight in ten patients required at least one change of their antifungal treatment, with an average of two changes per case and up to eight changes in certain cases. This observation highlights the complexities associated with the management of IMI in haematology patients, but also the important limitations of the available treatment options. More than half of those changes were prompted by clinical efficacy reasons, with lack of clinical improvement reported in the majority of cases, suggesting that worsening clinical presentations might have prompted treatment changes to achieve better outcomes. In a number of cases, treatment was changed as an effort to deescalate and/or adjust to clinical suspicion or targeted therapy. While broad-spectrum treatment may be preferred as first-line treatment for a possible IMI in order to cover for non-*Aspergillus* IMI, our data show that treatment is frequently adjusted following the identification of a pathogen, consistent with antifungal stewardship recommendations for treatment de-escalation.[24] Notably, subtherapeutic azole concentrations prompted an important number of changes, as previously reported.[25]

Although responsible for only one third of treatment changes, toxicities represent a major problem in the treatment of IMI. Notably, only five patients received isavuconazole in this study, making our observations on azoles predominately focused on voriconazole and posaconazole. Similarly, only liposomal amphotericin-B was used, limiting our observations to this agent only. As expected, hepatotoxicity, neurotoxicity and drug interactions were mainly associated with azole administration, while nephrotoxicity with liposomal amphotericin-B. Our observations come to further support data showing high rates of voriconazole prophylaxis discontinuation in allogeneic HCT recipients due to associated toxicities.[12,15,16] Patients with AML and allogeneic HCT recipients frequently have impaired renal or liver function due to—among others—volume depletion or overload, concomitant administration of other potentially nephrotoxic or hepatotoxic agents, liver GvHD or veno-occlusive disease. As a result, hepatotoxicity or nephrotoxicity is usually multifactorial. Hence, it is almost impossible to discern whether and at what degree antifungal treatments might have contributed to the observed organ dysfunction, particularly in the context of a retrospective observational study. However and despite lack of definitive causality links and mild to moderate liver test abnormalities, those treatments are often stopped by the treating physicians upon clinical suspicion of associated toxicities leading to important treatment interruptions. With azoles representing the major tool for the treatment of IA and other non-IA IMI, our observations further demonstrate the need for newer effective and safe therapies.

We hypothesised that treatment changes might have an effect on clinical outcomes. A trend for higher 12-week all-cause mortality was observed in those patients who had ≥2 treatment changes during the first 6 weeks of their treatment. Furthermore, the latter was associated with significantly higher 1-year mortality and was identified as the major mortality predictor in multivariable analyses with a fourfold increase in mortality by one year. It is likely that patients requiring more treatment changes were sicker with more comorbidities, more likely to have renal and/or liver dysfunction and require co-administration of multiple agents leading to higher rates of toxicities and mortality. However, a potential negative effect of treatment changes and interruptions, as well as treatment-related toxicities on clinical outcomes cannot definitively be ruled out. This is even more pertinent for azoles, agents requiring longer periods of time to attain therapeutic drug levels and steady state.[13,25–30] Finally, co-administration of strong CYP3A4 azole inhibitors, such as voriconazole and posaconazole, with midostaurin, venetoclax or other new chemotherapies may lead to treatment-related toxicities and unfavourable outcomes.[31] Although a potential effect of IMI on mortality cannot be ruled out, attributing mortality in the setting of a retrospective study and particularly as late as 12 weeks and 1 year post-IMI diagnosis would be associated with many potential biases, hence this was not included in our objectives.

Delays to treatment or appropriate antifungal treatment initiation have been associated with dismal clinical outcomes in patients with candidemia, while early diagnosis of IA based on a 'halo sign' has been associated with improved survival due to early treatment initiation.[32–34] Similar to previously reported data, we report higher 12-week mortality in patients with IMI, whose treatment was started after a week from IMI diagnosis.[35] For the purposes of this study, the day of IMI diagnosis was considered as the day the first diagnostic test was obtained. Hence, treatment initiation could have been delayed until a microbiology result was available. Moulds, particularly *Mucorales* and some slowly sporulating *Aspergillus* spp., may take several days to grow in the microbiology laboratory.[36–39] Furthermore, PCR is performed at a reference laboratory for our institution and the turnaround time for test results might have further delayed establishing a diagnosis. Those logistical delays might have been, in part, associated with lack of prompt treatment initiation. It is also likely, that in a number of cases clinicians might have been hesitant to initiate empirical antifungal treatment based on a lower clinical suspicion for an IMI and underlying host comorbidities, in an effort to optimise the risk-benefit ratio by avoiding potential antifungal treatment-associated toxicities. Time to appropriate treatment initiation was also strongly associated with higher 12-week all-cause mortality. A longer time to appropriate treatment initiation was observed for non-IA IMI versus IA. This further underscores the difficulty to obtain a microbiological diagnosis for non-IA IMI and hence the time-lag to initiate appropriate treatment for the management of those infections.

This study has important limitations, including its single-centre retrospective design and the small number of IMI included. Due to lack of standardisation of treatment change causes, we tried to use clinically relevant definitions, in order to be able to include and categorise most reasons of antifungal treatment changes in a consistent and generalisable manner. In conclusion, we report long treatment courses for the management of IMI, requiring multiple treatment

changes due to variable reasons and potential effects on clinical outcomes. Our findings further point to the limitations of the current antifungal therapy landscape and the urgent need for effective and safer treatment options.

ACKNOWLEDGEMENTS

The authors would like to thank all our colleagues, nurses and physicians for taking care of the patients in the transplant inpatient and outpatient units. Open Access Funding provided by Universite de Geneve.

CONFLICT OF INTEREST

RR, S.M-L., FG, A-CM, EG, FL, P-Y. B., VE, SE, C.v.D., and LK have no conflicts of interest. YC has received consulting fees from MSD. DN has received research support from MSD and Pfizer and consulting fees from Roche Diagnostics, MSD, Pfizer, Basilea, and Gilead.

AUTHOR CONTRIBUTIONS

Romain Samuel Roth: Conceptualization (equal); Data curation (equal); Formal analysis (lead); Investigation (lead); Methodology (equal); Writing – original draft (lead). **Stavroula Masouridi-Levrat:** Investigation (supporting); Writing – review & editing (supporting). **Federica Giannotti:** Investigation (supporting); Writing – review & editing (supporting). **Anne-Claire Mamez:** Investigation (supporting); Writing – review & editing (supporting). **Emmanouil Glampedakis:** Investigation (supporting); Writing – review & editing (supporting). **Frederic Lamoth:** Investigation (supporting); Writing – review & editing (supporting). **Pierre-Yves Bochud:** Investigation (supporting); Writing – review & editing (supporting). **Veronique Erard:** Investigation (supporting); Writing – review & editing (supporting). **Stephane Emonet:** Investigation (supporting). **Christian van Delden:** Investigation (supporting); Writing – review & editing (supporting). **Laurent Kaiser:** Investigation (supporting); Writing – review & editing (supporting). **Yves Chalalndon:** Investigation (supporting); Writing – review & editing (supporting). **D. Neofytos:** Conceptualization (equal); Data curation (equal); Formal analysis (supporting); Funding acquisition (lead); Investigation (equal); Methodology (equal); Project administration (equal); Resources (equal); Validation (equal); Writing – original draft (supporting).

DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Roth RS, Masouridi-Levrat S, Giannotti F, et al. Frequency and causes of antifungal treatment changes in allogeneic haematopoïetic cell transplant recipients with invasive mould infections. *Mycoses*. 2022;65:199–210. doi:10.1111/myc.13416