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ORIGINAL RESEARCH

Systemic Antifungal Prophylaxis in Patients Hospitalized in Hematology Units in France: The AFHEM Cross-Sectional Observational Study

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ABSTRACT

Introduction: The frequency of invasive fungal diseases (IFDs) has increased in recent years. Within a context where both treatments and guidelines are fast evolving, we aim to shed new light on IFD management in hematologic departments in France.

Methods: A multicenter cross-sectional observational study was prospectively conducted in 24 French centers in September and October 2013.

Results: Four hundred ninety-four hospitalized children and adult patients suffering from hematologic malignancy were enrolled: 147 (30%) were allogeneic hematopoietic stem cell transplant (HSCT) recipients, 131 (27%) were patients with acute myeloblastic leukemia or myelodysplastic syndrome (MDS), 71 (14%) were patients with acute lymphoblastic leukemia who did not undergo allogeneic HSCT, and the 145 (29%) remaining patients did not belong to the three above groups. Two hundred forty-six patients (50%) received antifungal treatment, which was prophylactic in 187 (76%) treated patients. These rates were similar across all groups (63–80%). Patients received prophylaxis with an azole (79%), intravenous amphotericin B formulation (10%), echinocandin (9%), or two combination drugs (2%).

Conclusion: Results indicate that prophylaxis is the leading antifungal strategy in French hematology units, regardless of the disease condition, representing 76% of prescriptions for antifungal therapy.

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INTRODUCTION

The frequency of invasive fungal diseases (IFD) has increased dramatically within the last few years mainly because of the growing number of immunocompromised patients [1]. *Candida* sp. and *Aspergillus* sp. are the main pathogenic fungal agents that may lead to severe infectious complications particularly in neutropenic patients, recipients of allogeneic hematopoietic stem cells transplants (HSCT), or solid organ transplants, as well as patients in intensive care units presenting with multiple risk factors (e.g., broad-spectrum antibiotics, intravascular catheters, kidney failure, dialysis, long-term intubation) [2, 3]. In addition, the mortality rate associated with IFD remains very high ($\geq$ 40%) [4].

IFDs are difficult to diagnose and treat although various clinical guidelines have been published in the US by the Infectious Diseases Society of America [5], in Europe by the European Conference on Infections in Leukaemia (ECIL) [6] and the European Society of Clinical Microbiology and Infectious Diseases [7], and in various countries [8–12] to help physicians in their practices.

Antifungal drugs are used according to four different approaches: (1) prophylaxis for patients with a high risk of developing an IFD but without apparent symptoms [13–16]; (2) empiric treatment for patients with suspected fungal infection in the absence of radiologic, microbiologic, histologic, or serologic evidence, which is a widely used strategy for neutropenic patients with persistent fever after 4–7 days under broad-spectrum antibiotics or who become febrile after a period of apyrexia [17, 18]; (3) preemptive (also called diagnostic-driven) treatment where there is a high suspicion of IFD in high-risk patients with some radioclinical or biomarker evidence [19], including possible IFD, according to the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) criteria [20]; or (4) curative treatment for probable or proven IFD according to the EORTC/MSG criteria [20].

Within a context where both treatments and guidelines are fast evolving, this cross-sectional observational study aims to shed new light on IFD management in pediatric and adult hematologic units in France, describing the frequency of systemic antifungal prophylaxis, the characteristics of patients receiving antifungal prophylaxis, and the prescription practices used in clinical practice.

METHODS

Study Design and Patients

This was an observational, cross-sectional study carried out over 5 consecutive days in 2013. Although major changes in practices occurred when the empirical strategy emerged in the 2000s and then anti-filamentous chemoprophylaxis in 2007, we consider that practices changed only slightly between 2013 and 2018 and therefore this does not invalidate our observations. French hematologic units located in university hospital and medical cancer centers were invited to participate. All patients (children or adults) with hematologic malignancy hospitalized in participating hematologic units during the 5-day observational period and who gave their written informed consent were included in the study. No other selection criterion was applied. Each center participated in the study over 5 consecutive days, but due to organizational considerations, centers did not all participate in the study within the same period, and patient recruitment was spread over a period of 6 weeks.

Data Source

Data were entered by investigators or their staff on electronic case report forms (eCRFs),

including antifungal strategies at inclusion, hospitalization conditions, IFD history, hematologic malignancy and underlying conditions, antifungal treatments and other ongoing treatments, and IFD classification established by the physician. Clinical signs, imaging, and other examinations related to IFD episodes were collected for the patients who received preemptive or curative treatment. All data were recorded through a secure online case report form.

Compliance with Ethics Guidelines

The data were anonymized before any analysis occurred. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study. According to French regulatory requirements, approvals from the French review boards (Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé and Commission Nationale de l'Informatique et des Libertés) were obtained.

Statistical Analyses

The statistical analyses performed were mainly descriptive. The variables were analyzed according to the following general rules: quantitative variables were described by the number of available and missing data, mean, standard deviation, first quartile, median, third quartile, and minimum and maximum; qualitative and ordinal variables were described by the number of available and missing data, frequency, and percentage (of the total number of values available) of each modality. Confidence intervals (CIs) at 95% were calculated according to Wilson's method (with continuity correction). Subgroup analyses were performed according to the last systemic antifungal therapeutic strategy reported for patients treated at least 1 day during the 5 observation days. Antifungal prophylaxis was also described as primary (i.e., in the absence of a history of IFD) or secondary prophylaxis (in patients with a history of an IFD). A logistic regression model was used to determine the factors impacting the treatment with antifungal drugs. Multivariate analysis was preceded by univariate analysis; significant factor at the threshold of the univariate analysis was then introduced. It was based on conventional univariate statistical tests: distributions of qualitative variables were compared using the χ^2 test or Fisher's exact test if the expected frequency in any of the cells of the contingency table was less than five. A stepwise selection method (forward and backward combination of methods) was used to automatically select the most appropriate factors to take the model factors into account.

All analyses were carried out using SAS 9.2 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Participating Centers

Of the 31 French hematologic centers that initially agreed to participate in the study, 24 contributed patients. These active units had a total of 717 beds including 368 rooms with air treatment.

Twenty-two units were in university hospitals, and the two others were in medical cancer centers. Sixteen units were adult, and eight were pediatric. Two units were exclusively adult HSCT units.

Patients

Four hundred ninety-four patients were enrolled in the study between 16 September 2013 and 25 October 2013.

Most patients (87%) were adults, 288 (58%) suffered from acute leukemia, and 41 (8%) and 147 (30%) were recipients of autologous or allogeneic HSCT, respectively. Among those who received an allogeneic HSCT, 123 (84%) had recently been allo-transplanted (for less than 6 months). Thirty-seven percent of the patients were in relapse or refractory phase, and 231 (47%) were in partial or complete remission. Neutropenia was present for at least

10 days in 127 patients (26%), and 50 patients (10%) had a persistent fever refractory to antibiotic therapy. Three hundred forty-six patients (70%) had been hospitalized in the unit for less than 15 days. A total of 313 patients (63%) entered a room with air treatment, most of them (89%) since their first day of entry in the unit: 172 patients (55%) were placed in a laminar air flow room or Immunair™ bed, 88 patients (28%) in a highly purified HEPA-filtered room, and 53 (17%) in a conventional room with Plasmair™ or the equivalent. Thirteen percent of the patients had already experienced an IFD episode.

These 494 patients were classified into four groups: group 1 included the allogeneic HSCT recipients (n = 147), group 2 included patients suffering from acute myeloblastic leukemia (AML) or myelodysplastic syndrome (MDS) (n = 131), group 3 included patients suffering from acute lymphoblastic leukemia (ALL) (n = 71), and group 4 included all patients not included in groups 1, 2, or 3 (n = 145). Their characteristics are summarized in Table 1.

The demographic characteristics of the patients belonging to groups 1, 2, and 4 were similar. Because the patients from group 3 presented with ALL, this group included more children than the other groups (48%), and the median age of adult patients was lower (39.8 years in group 3 versus 51.0, 58.0, and 64.6 years in groups 1, 2, and 4, respectively). Regarding ongoing treatments, patients from group 1 were more likely to be treated with antibiotics (85%), antiviral agents (88%), and immunosuppressive treatments (69%). Moreover, they were more often placed in a sterile room, a laminar air flow room, Immunair™ bed, or highly purified HEPA-filtered room (82% vs. 60, 41, and 22% for groups 2, 3, and 4, respectively).

Regarding the 64 (13%) pediatric patients enrolled in the study, they had mean age of 8.4 years and were mainly suffering from ALL [32 patients (50%)] or AML [20 patients (31%)]. Less than 20% (12 patients) were HSCT recipients. Nineteen percent of the patients were in the relapse or refractory phase, and 38 (59%) were in partial or complete remission. Neutropenia was present for at least 10 days in 17 patients (27%), and 6 patients (9%) had a persistent fever refractory to antibiotic therapy. Their characteristics are summarized in Table 2.

Antifungal Strategies

The frequency of antifungal treatment was 50% (95% CI 45.3–54.3), i.e., 246 patients received a systemic antifungal treatment (as a prophylactic, empiric, preemptive, or curative strategy) during at least 1 of the 5-day observational periods.

The frequency of antifungal strategies is presented in Table 3 for each of the four groups. One hundred eighty-seven (38%) patients received antifungal prophylaxis, representing 76% of treated patients. The proportions of patients who received antifungal prophylaxis among those treated with antifungal agents were similar in the four groups: 80% in group 1, 72% in group 2, 63% in group 3, and 80% in group 4. Primary antifungal prophylaxis was delivered to 145 patients (78% of the patients who received antifungal prophylaxis), and the remaining 42 patients received secondary antifungal prophylaxis. The frequency of secondary prophylaxis was higher in group 4 than in the other groups.

The frequency of antifungal strategies according to age group (i.e., adults and pediatrics) is presented in Table 2. Of the 64 pediatric patients included in the study, 20 (31%) were treated with systemic antifungals; 13 received antifungal prophylaxis (mainly primary prophylaxis; 10 patients), representing 65% of treated patients.

Characteristics of Patients Receiving Antifungal Prophylaxis

Characteristics of the 187 patients who received antifungal prophylaxis are summarized in Table 4. Half of the patients from groups 2 and 3 (patients with AML, ALL, or MDS) presented with neutropenia for at least 10 days when enrolled in the study compared with 17% for groups 1 and 4. Of the 95 patients treated with antifungal prophylaxis who had received allogeneic HSCT, 40% were in a neutropenic phase,

Table 1 Characteristics of patients according to the pathology profile

	Group 1 ***n*** **= 147**	**Group 2** ***n*** **= 131**	**Group 3** ***n*** **= 71**	**Group 4** ***n*** **= 145**	**Total** ***n*** **= 494**
Gender (male)	79 (54)	83 (63)	36 (51)	89 (61)	287 (58)
Adults	1[35 (92)]	117 (89)	44 (62)	134 (92)	430 (87)
Age, years, median					
Adult (range)	51.0 (21–71)	58.0 (23–86)	39.8 (18–70)	64.6 (24–90)	56.8 (18–90)
Children (range)	6.3 (0–12)	8.9 (1–17)	10.5 (1–17)	8.8 (0–16)	8.4 (0–17)
Hematologic malignancy					
Acute myeloid leukemia	67 (46)	125 (95)			192 (39)
Myelodysplastic syndrome	8 (5)	6 (5)			14 (3)
Acute lymphoblastic leukemia	25 (17)		71 (100)		96 (19)
Hodgkin lymphoma	13 (9)			13 (9)	26 (5)
Non-Hodgkin lymphoma	11 (7)			83 (57)	94 (19)
Chronic lymphoid leukemia	1 (1)			11 (8)	12 (2)
Myeloma	9 (6)			32 (22)	41 (8)
Chronic myeloid leukemia	6 (4)				6 (1)
Other	7 (5)			6 (4)	13 (3)
Disease status (relapse or refractory)	92 (64)	17 (13)	12 (17)	60 (41)	181 (37)
Underlying conditions					
Autologous transplant	0	1 (1)	2 (3)	38 (26)	41 (8)
Allogeneic transplant[a]	147 (100)				147 (30)
GVHD[b,c]	47 (32)				47 (32)
Grade I–II acute GVHD	23				23
Grade III–IV acute GVHD	18				18
Chronic GVHD	13				13
Neutropenic phase[c]	64 (44)				64 (44)
ANC < 0.5, 10/l for at least 10 days	35 (24)	62 (47)	20 (28)	10 (7)	127 (26)
Persistent fever refractory to antibiotic therapy	15 (10)	20 (15)	5 (7)	10 (7)	50 (10)
Previous IFD	33 (22)	17 (13)	9 (13)	3 (2)	62 (13)
Ongoing treatments					
Chemotherapy	63 (43)	106 (81)	60 (85)	98 (68)	327 (66)
Antibiotics	125 (85)	104 (79)	48 (68)	92 (63)	369 (75)

Table 1 continued

	Group 1 *n* = 147	Group 2 *n* = 131	Group 3 *n* = 71	Group 4 *n* = 145	Total *n* = 494
Immunosuppressors	102 (69)	10 (8)	22 (31)	27 (19)	161 (33)
Antivirals	130 (88)	73 (56)	33 (47)	79 (54)	315 (64)
Time since entry in the unit					
≥ 30 days	37 (25)	19 (15)	8 (11)	7 (5)	71 (14)
Between 15 and 29 days	25 (17)	32 (24)	11 (15)	9 (6)	77 (16)
< 15 days	85 (58)	80 (61)	52 (73)	129 (89)	346 (70)
Hospitalization in room with air treatment	127 (86)	99 (76)	39 (55)	48 (33)	313 (63)
Laminar air flow room or Immunair™ bed[d]	96 (76)	48 (49)	18 (46)	10 (21)	172 (55)
Highly purified HEPA-filtered room[d]	24 (19)	31 (31)	11 (28)	22 (46)	88 (28)
Conventional room with plasmair™ or equivalent[d]	7 (5)	20 (20)	10 (26)	16 (33)	53 (17)

Data are *n* (%), unless otherwise specified

ANC absolute neutrophil count, *GVHD* graft-versus-host disease, *IFD* invasive fungal disease

[a] 123 patients transplanted for less than 6 months

[b] Chronic and/or acute GVHD

[c] Percentage among recipients of allogeneic hematopoietic stem cell transplant

[d] Percentage among patients hospitalized in a room with air treatment

10% had developed acute grade I–II graft-versus-host disease (GVHD), 15% had acute grade III–IV GVHD, and 7% presented with chronic GVHD. One hundred fifty-seven patients were placed in a room with air treatment, with a similar proportion in each of the four groups. However, of the 88% of patients in a room with sterile air treatment (in the laminar air flow room, Immunair™ bed, or highly purified HEPA-filtered room), there were proportionately more patients from group 1 than in the other groups. Nineteen patients who received antifungal prophylaxis did not enter a sterile room, but were only placed in a conventional room with Plasmair™ or the equivalent.

Factors associated with prophylactic strategy were researched using a logistic regression model among the 246 treated patients. The results of univariate analysis are presented in Table 5. Multivariate analysis showed that allogeneic HSCT (OR 4.57, 95% CI 2.47–8.47; $p < 0.0001$), AML or MDS (OR 3.07, 95% CI 1.68–5.61; $p < 0.0001$), antiviral treatment (OR 3.46, 95% CI 2.11–5.67; $p < 0.0001$), and entry in a sterile room (OR 2.39, 95% CI 1.51–3.79; $p < 0.0002$) were associated with systemic antifungal prophylaxis prescription.

Antifungal Drugs Prescribed

Antifungal drugs prescribed to patients who received antifungal prophylactic strategy are presented in Table 6. Overall, 79% of the patients who received antifungal prophylaxis during the 5-day observational period were administered an azole, 10% an intravenous amphotericin B formulation, 9% an echinocandin, and 2% a combination of two drugs. The most commonly used prophylactic drugs were fluconazole (administered to 41% of the patients who received prophylaxis), posaconazole (29%), amphotericin B (11%: liposomal 7%, conventional 4%), voriconazole (9%), caspofungin (7%), and micafungin (3%).

Table 2 Main patient's characteristics and systemic antifungal strategy according to age group

	Adults ***n*** **=430**	**Pediatrics** ***n*** **=64**	**Total** ***N*** **=494**
Patient's characteristics			
Hematologic malignancy			
Acute myeloid leukemia	172 (40)	20 (31)	192 (39)
Myelodysplastic syndrome	14 (3)		14 (3)
Acute lymphoblastic leukemia	64 (15)	32 (50)	96 (19)
Hodgkin lymphoma	24 (6)	2 (3)	26 (5)
Non-Hodgkin lymphoma	85 (20)	9 (14)	94 (19)
Chronic lymphoid leukemia	12 (3)		12 (2)
Myeloma	41 (10)		41 (8)
Chronic myeloid leukemia	5 (1)	1 (2)	6 (1)
Other	13 (3)		13 (3)
Disease status (relapse or refractory)	169 (39)	12 (19)	181 (37)
Underlying conditions			
Autologous transplant	41 (10)		41 (8)
Allogeneic transplant[a]	135 (31)	12 (19)	147 (30)
Acute GVHD[b]	35 (26)	6 (50)	41 (28)
Neutropenia for at least 10 days	110 (26)	17 (26)	127 (26)
Persistent fever refractory to antibiotic therapy	44 (10)	6 (9)	50 (10)
Previous IFD	57 (13)	5 (8)	62 (13)
Ongoing treatments			
Chemotherapy	272 (63)	55 (86)	327 (66)
Antibiotics	326 (76)	43 (67)	369 (75)
Immunosuppressors	136 (32)	25 (39)	161 (33)
Antivirals	303 (70)	12 (19)	315 (64)
Time since entry in the unit			
$\geq$ 30 days	62 (14)	9 (14)	71 (14)
Between 15 and 29 days	63 (15)	14 (22)	77 (16)
$<$ 15 days	305 (71)	41 (64)	346 (70)
Hospitalization in room with air treatment	281 (65)	32 (50)	313 (63)
Laminar air flow room or Immunair^{TM} bed[c]	149 (53)	23 (72)	172 (55)
Highly purified HEPA-filtered room[c]	79 (28)	9 (28)	88 (28)
Conventional room with Plasmair^{TM} or equivalent[c]	53 (19)		53 (17)

Table 2 continued

	Adults *n* =430	Pediatrics *n* =64	Total *N* =494
Systemic antifungal strategy			
Not treated with systemic antifungals	204 (47)	44 (69)	248 (50)
Treated with systemic antifungals	226 (53)	20 (31)	246 (50)
Prophylactic strategy[d]	174 (77)	13 (65)	187 (76)
Primary[e]	135 (78)	10 (77)	145 (78)
Secondary[e]	39 (22)	3 (23)	42 (22)
Empiric strategy[d]	20 (9)	5 (25)	25 (10)
Preemptive or curative strategy[d]	32 (14)	2 (10)	34 (14)

Data are *n* (%), unless otherwise specified

GVHD graft-versus-host disease, *IFD* invasive fungal disease

[a] 123 patients (114 adults and 9 pediatric patients) transplanted for less than 6 months

[b] Percentage of recipients receiving allogeneic hematopoietic stem cell transplant

[c] Percentage of patients hospitalized in room with air treatment

[d] Percentage of patients treated with systemic antifungals

[e] Percentage of patients receiving a systemic antifungal prophylactic strategy

Table 3 Frequency of systemic antifungal strategies according to the pathology profile

	Group 1 *n* = 147	Group 2 *n* = 131	Group 3 *n* = 71	Group 4 *n* = 145	Total *n* = 494
Not treated with systemic antifungals	28 (19)	53 (40)	52 (73)	115 (79)	248 (50)
Treated with systemic antifungals	119 (81)	78 (60)	19 (27)	30 (21)	246 (50)
Prophylactic strategy[a]	95 (80)	56 (72)	12 (63)	24 (80)	187 (76)
Primary[b]	75 (79)	48 (86)	10 (83)	12 (50)	145 (78)
Secondary[b]	20 (21)	8 (14)	2 (17)	12 (50)	42 (22)
Empiric strategy[a]	13 (11)	6 (8)	2 (11)	4 (13)	25 (10)
Preemptive or curative strategy[a]	11 (9)	16 (20)	5 (26)	2 (7)	34 (14)

Data are *n* (%)

[a] Percentage among patients treated with systemic antifungals

[b] Percentage among patients receiving a systemic antifungal prophylactic strategy

Slight differences were observed when comparing the patients who received primary prophylaxis (*n* =145) to those who received secondary prophylaxis (*n* =42): posaconazole and fluconazole were administered to 73% of the patients receiving primary prophylaxis versus 60% of the patients receiving secondary prophylaxis, while voriconazole (either oral or intravenous) was administered to 4% of the patients receiving primary prophylaxis versus 24% of those receiving secondary prophylaxis (Table 7).

Table 4 Characteristics of hospitalized patients receiving systemic antifungal prophylaxis according to the pathology profile

	Group 1 ***n*** **= 95**	**Group 2** ***n*** **= 56**	**Group 3** ***n*** **= 12**	**Group 4** ***n*** **= 24**	**Total** ***n*** **= 187**
Gender (male)	56 (59)	32 (57)	10 (83)	14 (58)	112 (60)
Adults	88 (93)	53 (95)	10 (83)	23 (96)	174 (93)
Age, year, median					
Adult (range)	52.2 (21–71)	54.0 (23–81)	34.9 (21–67)	55.2 (24–67)	52.7 (21–81)
Children (range)	7.7 (0–12)	10.8 (10–14)	6.9 (3–11)	0.5 (NA)	7.9 (0–14)
Hematologic malignancy					
Acute myeloid leukemia	41 (43)	56 (100)			97 (52)
Myelodysplastic syndrome	5 (5)				5 (3)
Acute lymphoblastic leukemia	16 (17)		12 (100)		28 (15)
Hodgkin lymphoma	9 (9)			2 (8)	11 (6)
Non-Hodgkin lymphoma	9 (7)			11 (46)	20 (11)
Chronic lymphoid leukemia	1 (1)				1 (1)
Myeloma	5 (5)			9 (38)	14 (7)
Chronic myeloid leukemia	3 (3)				3 (2)
Other	6 (6)			2 (8)	10 (5)
Disease status (relapse or refractory)	56 (59)	6 (11)	4 (33)	11 (46)	77 (41)
Underlying conditions					
Autologous transplant	0	0	0	15 (63)	15 (8)
Allogeneic transplant[a]	95 (100)	0	0	0	95 (51)
GVHD[b,c]	27 (28)				27 (28)
Grade I–II acute GVHD	10				10
Grade III–IV acute GVHD	14				14
Chronic GVHD	7				7
Neutropenic phase[c]	38 (40)				38 (40)
ANC < 0.5, 10/l for at least 10 days	16 (17)	28 (50)	6 (50)	4 (17)	54 (29)
Persistent fever refractory to antibiotic therapy	6 (6)	7 (13)	1 (8)	1 (4)	15 (8)
Previous IFD	19 (20)	8 (14)	2 (17)	0	29 (16)
Ongoing treatments					
Chemotherapy	44 (46)	49 (88)	12 (100)	8 (33)	113 (60)
Antibiotics	80 (84)	44 (79)	11 (92)	17 (71)	152 (81)

Table 4 continued

	Group 1 $n = 95$	Group 2 $n = 56$	Group 3 $n = 12$	Group 4 $n = 24$	Total $n = 187$
Immunosuppressants	67 (71)	3 (5)	6 (50)	2 (8)	78 (42)
Antivirals	87 (92)	39 (64)	10 (83)	20 (83)	156 (83)
Time since entry in the unit					
$\geq$ 30 days	20 (21)	33 (59)	2 (17)	1 (4)	30 (16)
Between 15 and 29 days	14 (15)	16 (29)	3 (25)	3 (13)	36 (19)
$<$ 15 days	61 (64)	7 (13)	7 (58)	20 (83)	121 (65)
Hospitalization in room with air treatment	82 (86)	48 (86)	9 (75)	18 (75)	157 (84)
Laminar air flow room or Immunair™ bed[d]	60 (73)	22 (46)	2 (22)	1 (6)	85 (54)
Highly purified HEPA-filtered room[d]	18 (22)	19 (40)	4 (44)	12 (67)	53 (34)
Conventional room with Plasmair™ or equivalent[d]	4 (5)	7 (14)	3 (33)	5 (28)	19 (12)

Data are *n* (%), unless otherwise specified

ANC absolute neutrophil count, *GVHD* graft-versus-host disease, *IFD* invasive fungal disease

[a] 82 patients transplanted for less than 6 months

[b] Chronic and/or acute GVHD

[c] Percentage among recipients of allogeneic hematopoietic stem cell transplant

[d] Percentage among patients hospitalized in a room with air treatment

DISCUSSION

The AFHEM study was the first cross-sectional observational study to determine the use of antifungal treatment strategies used in hematologic patients in medical practice in France. Half of the patients hospitalized in hematology centers received a systemic antifungal agent (53% in adults and 31% in pediatric patients), and prophylaxis was the leading strategy used.

Guidelines and expert committees suggest risk stratifying patients from very low risk to very high risk of developing IFD to determine the most appropriate antifungal strategy [6, 11, 21]. Unfortunately, there is no uniformity across the guidelines for the criteria for each group. In this study, the proportion of patients receiving systemic antifungal prophylaxis ranged from 17% to 65% of the whole population and from 63% to 80% of patients treated with antifungals, depending on the risk level for IFD. Interestingly, 81% of patients who received prophylaxis were either allogeneic HSCT patients or AML patients, and these indications are therefore in accordance with international recommendations.

Azoles are recommended for prophylaxis in high-risk patients [5, 6, 9–11]. Guidelines from ECIL [6] and the German Society for Hematology and Medical Oncology [22] recommend that the choice of antifungal agent is based on clinical indication. For example, during the neutropenic phase following an allogeneic transplant, fluconazole is recommended for patients at low risk of developing invasive aspergillosis, but this is to be switched in patients at high risk of invasive aspergillosis (to voriconazole) or if patients develop GVHD (to posaconazole). We found that oral or intravenous fluconazole was the predominant drug used during the neutropenic phase in HSCT patients to prevent invasive candidiasis combined with sterile air conditions in to prevent IFD due to filamentous fungi, as mentioned above. Of note, if fluconazole is chosen, there is also a need for a mold-directed diagnostic

Table 5 Factor associated with antifungal prophylactic strategy: univariate analysis

	No antifungal prophylactic strategy *n* =307	**Antifungal prophylactic strategy *n* =187**	***p* value***
Pathology profile			
Group 1	52 (17)	95 (51)	< 0.001 (S)
Group 2	75 (24)	56 (30)	
Group 3	59 (19)	12 (6)	
Group 4	121 (39)	24 (13)	
Gender			
Male	175 (57.)	112 (60)	0.528 (NS)
Female	132 (43)	75 (40)	
Age group			
Pediatrics	51 (17)	13 (7)	0.002 (S)
Adults	256 (83)	174 (93)	
Entry in a sterile room[a]			
No	185 (60%)	49 (6%)	< 0.001 (S)
Yes	122 (40%)	138 (74%)	
First-line treatment			
No	115 (38)	75 (40)	0.557 (NS)
Yes	192 (62)	112 (60)	
Disease status			
Missing values	2	2	
Initial phase	201 (66)	108 (58)	0.094 (NS)
Relapse/refractory	104 (34)	77 (42)	
ANC < 0.5, 10/l for at least 10 days			
Missing values	1	0	
No	233 (76)	133 (71)	0.216 (NS)
Yes	73 (24)	54 (29)	
Persistent fever refractory to antibiotherapy			
No	272 (89)	172 (92)	0.227 (NS)
Yes	35 (11)	15 (8)	
Previous IFD			
No	274 (89)	158 (85)	0.121 (NS)
Yes	33 (11)	29 (15)	

Table 5 continued

	No antifungal prophylactic strategy*n* =307	Antifungal prophylactic strategy*n* =187	*p* value*
Ongoing chemotherapy			
No	93 (30)	74 (40)	0.034 (S)
Yes	214 (70)	113 (60)	
Ongoing antibiotherapy			
No	90 (29)	35 (19)	0.009 (S)
Yes	217 (71)	152 (81)	
Ongoing immunosuppressive treatment			
No	224 (73)	109 (58)	0.001 (S)
Yes	83 (27)	78 (42)	
Ongoing antiviral treatment			
No	148 (48)	31 (17)	< 0.001 (S)
Yes	159 (52)	156 (83)	
Ongoing monoclonal antibody			
No	288 (94)	183 (98)	0.038 (S)
Yes	19 (6)	4 (2)	

Data are *n* (%)
ANC absolute neutrophil count, *IFD* invasive fungal disease
*Pearson χ^2 test (two sided)
[a] Sterile room is defined as Laminar flow sterile room, Immunair^{TM} bed, or highly purified HEPA-filtered room

strategy [7]. Consistent with recommendations for patients with AML or MDS receiving intensive chemotherapy, we found that posaconazole was the main drug (63%) used in this group of patients. The ECIL-3 guidelines also recommend voriconazole for both the neutropenic and GVHD phases in allogeneic HSCT settings. In our study, voriconazole was only rarely prescribed for prophylaxis, except in cases of secondary prophylaxis.

A French case-control study previously published in 2011 showed a significant association between prior exposure to caspofungin and an elevated risk of bloodstream infection caused by *Candida* spp. having reduced susceptibility to caspofungin in adults with hematologic malignancies [23]. Thus, considering these results and those published on azole resistance, use of antifungal medications always requires constant vigilance for resistance emergence, particularly during long-term prophylaxis.

Eighty-four percent of the patients receiving antifungal prophylaxis were hospitalized in rooms with air treatment, 88% of them being placed in a sterile room (in a laminar air flow room, Immunair^{TM} bed, or highly purified HEPA-filtered room), thus combining drug administration with environmental measures to prevent systemic infections and illustrating the appropriate perception of high-risk conditions by the clinicians. The low rate of empiric, preemptive, and curative therapies in groups 1 and 2 (20% and 28%, respectively) might be explained by the high level and rate of prophylactic strategies. Of note, empiric therapy is used more often in children (25%) than in adults (9%).

Table 6 Systemic antifungal prophylactic strategy: drugs administered according to the pathology profile

	Group 1 ***n*** **= 95**	**Group 2** ***n*** **= 56**	**Group 3** ***n*** **= 12**	**Group 4** ***n*** **= 24**	**Total** ***n*** **= 187**
Missing values	1 (1)	0	0	0	1 (0.5)
Azole alone	70 (74)	49 (88)	7 (58)	22 (92)	148 (79)
Amphotericin B formulation alone	10 (11)	5 (9)	2 (17)	1 (4)	18 (10)
Echinocandin alone	13 (14)	1 (2)	2 (17)	1 (4)	17 (9)
Amphotericin B formulation and azole	1 (1)	1 (2)	0	0	2 (1)
Amphotericin B formulation and echinocandin	0	0	1 (8)	0	1 (0.5)
Azole type					
N	71	50	7	22	150
PO fluconazole	38 (54)	5 (10)	4 (57)	16 (73)	63 (42)
IV fluconazole	6 (8)	3 (6)	0	4 (18)	13 (9)
PO posaconazole	16 (23)	35 (70)	3 (43)	1 (5)	55 (37)
PO voriconazole	8 (11)	4 (8)	0	0	12 (8)
IV voriconazole	3 (4)	1 (2)	0	0	4 (3)
Itraconazole	0	1 (2)	0	1 (5)	2 (1)
Posaconazole—PO voriconazole	0	1 (2)	0	0	1 (1)
Amphotericin B formulation					
N	11	6	3	1	21
IV liposomal amphotericin B	8 (73)	4 (67)	2 (67)	0	14 (67)
IV conventional amphotericin B	3 (27)	2 (33)	1 (33)	1 (100)	7 (33)
Echinocandin type					
N	13	1	3	1	18
Caspofungin	11 (85)	1 (100)	1 (33)	0	13 (72)
Micafungin	2 (15)	0	2 (67)	1 (100)	5 (28)

Data are *n* (%)

Although providing interesting information on patients receiving antifungal prophylaxis in French hematology units, our study has some limitations, mainly due to its design. First, we can assume that physician selection bias could also have led to patient selection bias. Indeed, physician participation was offered on a voluntary basis, and the final center sample may not be representative of the use of antifungal therapy in France. This potential bias is inevitable in this type of study, and its impact is difficult to evaluate. Moreover, even though the sample was comprehensive, the patients could refuse to participate in the study, and the final population may not be perfectly representative. To be included in the study, the patients (or their representative) were required to give their written approval. We established a registry to record the patients hospitalized in participating units and eligible for the study. Of the 158 patients recorded in the registry who did not give their written approval for participation in

Table 7 Systemic antifungal drugs prescribed according to the type of prophylactic strategy

	Primary prophylaxis ***n*** **=145**	**Secondary prophylaxis** ***n*** **=42**	**Total** ***n*** **= 187**
Missing values	1 (1)	0	1 (0.5)
Amphotericin B formulation alone	111 (77)	37 (88)	148 (79)
Amphotericin B alone	15 (10)	3 (7)	18 (10)
Echinocandin alone	15 (10)	2 (5)	17 (9)
Amphoterin B formulation and azole	2 (1)	0	2 (1)
Amphotericin B formulation and echinocandin	1 (1)	0	1 (0.5)
Azole type			
n	113	37	150
PO fluconazole	50 (44)	13 (35)	63 (42)
IV fluconazole	12 (11)	1 (3)	13 (9)
PO posaconazole	44 (39)	11 (30)	55 (37)
PO voriconazole	4 (4)	8 (22)	12 (8)
IV voriconazole	2 (2)	2 (5)	4 (3)
Itraconazole	1 (1)	1 (3)	2 (1)
Posaconazole—PO voriconazole	0	1 (3)	1 (1)
Amphotericin B formulation			
n	18	3	21
IV liposomal amphotericin B	11 (61)	3 (100)	14 (67)
IV conventional amphotericin B	7 (39)	0	7 (33)
Echinocandin type			
n	16	2	18
Caspofungin	12 (75)	1 (50)	13 (72)
Micafungin	4 (25)	1 (50)	5 (28)

Data are *n* (%)

the study (25%), 128 did not receive any antifungal drug. It can thus be assumed that the proportion of patients treated with a systemic antifungal drug could have been slightly overestimated.

CONCLUSION

This work provides a comprehensive picture of patients hospitalized in French hematology units and treated with antifungal prophylaxis. Prophylaxis is now the leading strategy used in hematology, whatever the disease conditions of the patients with overall 76% of patients managed in this way. Prophylaxis is mainly based on fluconazole and posaconazole. Fluconazole is still used in allogeneic HSCT patients, in most cases associated with protected environmental conditions. Posaconazole is mainly used in AML/MDS patients, but also in ALL patients where its use is off-label. Echinocandins are

mainly used in high-risk patients, and caspofungin is the most used echinocandin, although it is not licensed for prophylaxis. Antifungal stewardship programs are thus of prime interest to rationalize antifungal use [24]. As recently published [25], although neutropenia is common to almost all hematologic patients, other factors (low complete response probability due to an adverse karyotype in AML, high-dose dexametazone in ALL, allogeneic HSCT from donors other than a matched sibling donor) may play a key role in these patients and may help to design the most appropriate diagnostic workup and antifungal strategy.

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Compliance with Ethics Guidelines. The data were anonymized before any analysis occurred. All procedures followed were in accordance with the ethical standards of the responsible committee on human

experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for being included in the study. According to French regulatory requirements, approvals from the French review boards (Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé and Commission Nationale de l'Informatique et des Libertés) were obtained.

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