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Adherence to, and outcomes of, a galactomannan screening protocol in high-risk hematology patients

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ABSTRACT

Background A twice-weekly galactomannan (GM) screening protocol was implemented in high-risk hematology inpatients. Study objectives were to determine adherence to the protocol, use of selected resources, and patient outcomes.

Methods This retrospective cohort study compared outcomes of interest before and after implementation of GM screening. Adults undergoing matched related allogeneic hematopoietic stem-cell transplantation or induction chemotherapy for acute leukemia were eligible. Patients could be enrolled more than once and were evaluated as episodes. Adherence to the GM protocol was assessed in post-implementation episodes. Use of broad-spectrum antifungals (BSAFs), consultations (infectious diseases, respirology), and diagnostic procedures (computed tomography imaging, bronchoalveolar lavage) were compared between phases, as were the patient outcomes of all-cause mortality and clinical success (alive and not taking a BSAF).

Results Of 182 episodes consecutively screened, 70 per phase were enrolled. Clinical characteristics and duration of assessment were similar for the phases. Full or partial adherence to the protocol was observed in 61 post-implementation episodes (87%), with full adherence in 40 episodes (57%). More episodes in the pre-implementation phase than in the post-implementation phase involved receipt of BSAFs, consultations, and diagnostics (27% vs. 7%, $p = 0.02$; 46% vs. 26%, $p = 0.014$; and 46% vs. 31%, $p = 0.083$ respectively). Although mortality was similar in the two phases, clinical success at the final assessment was observed in fewer pre-implementation than post-implementation episodes (79% vs. 98%, $p < 0.001$).

Conclusions Implementation of a GM screening protocol was feasible and associated with significantly fewer episodes involving receipt of BSAFs and consultations, and with significantly more episodes showing clinical success.

Key Words Adherence, antifungals, consultations, diagnostics, galactomannan, hematology, mortality, screening

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INTRODUCTION

Invasive fungal disease (IFD) is a significant cause of morbidity and mortality in patients undergoing allogeneic hematopoietic stem-cell transplantation (allo-HSCT) and in those receiving chemotherapy for hematologic malignancies[1]. Empiric antifungal therapy to treat suspected IFD has been the standard of care for neutropenic patients who have persistent fever despite treatment with broad-spectrum antibacterials. However, the appropriateness of using fever as the only indicator for initiating antifungals has been challenged, because that approach might lead to overtreatment[2–6].

Development of noninvasive diagnostic markers, such as galactomannan (GM), β-D-glucan, and polymerase chain reaction methods, have led to interest in replacing empiric

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therapy with a pre-emptive approach for persistently febrile neutropenic patients[7–9]. The same approach might be an effective way to target antifungal use, thereby minimizing the risk of drug-related complications, resistance, and costs[1]. A meta-analysis comparing empiric and pre-emptive antifungal strategies in patients with hematologic malignancy who have a high risk of febrile neutropenia showed that the pre-emptive strategies were associated with lesser antifungal exposure without an increase in IFD-related or overall mortality[10].

The GM enzyme-linked immunosorbent assay is a noninvasive diagnostic test that detects circulating GM, a major constituent of the *Aspergillus* polysaccharide cell wall that is released during growth[11]. Detection of GM in various body fluids is included as a diagnostic criterion for probable invasive aspergillosis by the European Organisation for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group[12]. Prospective studies that have incorporated the GM assay as the sole non-culture-based marker into a diagnostic-driven pre-emptive strategy in patients with hematologic malignancy have demonstrated decreased use of empiric antifungals without an increase in mortality[1,9,13].

In 2011 at our centre, fluconazole prophylaxis became a standard of care for inpatients undergoing either allo-HSCT or induction chemotherapy for acute leukemia who are at high risk of IFD. In December 2013, a twice-weekly GM screening protocol was implemented in the same population. The primary objective of the present study was to determine adherence to the GM screening protocol. Secondary objectives were to compare patient outcomes and the use of broad-spectrum antifungals (BSAFS) and consultative and diagnostic services before and after implementation of GM screening.

METHODS

Design and Study Population

This retrospective cohort study enrolled adult hematology patients at high-risk of IFD admitted to the Hematology Service of the London Health Sciences Centre, a tertiary care centre in London, Ontario. The Western University Office of Research Ethics reviewed and exempted the submission from the need for ethics approval because the study fulfilled the criteria of a quality improvement initiative.

Patients were eligible for inclusion if they were 18 years of age or older and were undergoing matched related allo-HSCT or induction chemotherapy for acute myeloid leukemia (AML) or acute lymphoid leukemia (ALL). Patients could be included in the study more than once, and therefore the assessment considered patient episodes. An "episode" referred to a patient admission beginning on day 0 of stem-cell infusion for allo-HSCT or on day 1 of induction chemotherapy for AML or ALL and continuing until either white cell count recovery (absolute neutrophil count 0.5×10^9/L or greater, or total peripheral leucocyte count 1×10^9/L or greater if a neutrophil count was not available), discharge, death, or the start of the next chemotherapy cycle, whichever occurred first. Exclusion criteria were death occurring before the first protocol day of GM screening, receipt of at least 3 consecutive days of BSAF during the week before the start of the episode, or the availability of a GM result from an external centre during the episode.

Episodes were identified from computerized pharmacy records for specific chemotherapy protocols defined *a priori* and prescribed during the study periods. Episodes in the phase before implementation of the GM protocol were consecutively screened for inclusion (September 2013 backward) until a convenience sample, based on available study resources, of 70 episodes was reached. Similarly, 70 episodes were enrolled for the phase after implementation of the GM protocol (February 2014 forward). The 4-month interruption between the "before" and "after" phases allowed for the implementation of GM screening in December 2013 and for a period of clinician adjustment to the new protocol through to the end of January 2014. Care decisions with respect to a patient's drug therapy, consultations, and diagnostics were at the discretion of clinicians in both study phases.

Data Collection

An electronic data collection tool was developed and piloted over a 4-week period. Operational definitions were established *a priori*, and data collection was performed by a single investigator. A quality audit of the data collected for 10% of the episodes in both phases was performed independently by a co-investigator not involved in the original data collection.

These data were captured from electronic and paper medical records: age, sex, hematologic diagnosis, neutropenia (defined as an absolute neutrophil count of $<0.5\times10^9$/L or a total peripheral leucocyte count of $<1\times10^9$/L if a neutrophil count was not available), targeted medications (chemotherapy, antifungals, broad-spectrum antibiotics), consultations (infectious diseases, respirology), diagnostic procedures (GM screens, computed tomography imaging, bronchoalveolar lavage), hospital discharge, and death. The indication for antifungals was determined from a review of the health record during the 3-day period before and after the prescription. Occurrence of a complication attributed to a BSAF was identified during the 3-day period before and after antifungal discontinuation, switch to an alternative agent, or change in dose.

Study Outcomes

The primary outcome was the proportion of episodes with adherence (full and partial) to the GM screening protocol in the post-intervention phase. "Full adherence" referred to the performance of all recommended twice-weekly screens during the episode or until 2 consecutive serum samples with a GM index of 0.5 or greater were attained. "Nonadherence" referred to no GM screens being performed. "Partial adherence" referred to episodes having other than full adherence or nonadherence.

Secondary outcomes included the proportion of episodes in the pre- and post-implementation phases involving receipt of a BSAF (amphotericin B, voriconazole, or caspofungin) for at least 3 consecutive days; consultations (infectious diseases, respirology) and diagnostic procedures (computed tomography imaging, bronchoalveolar lavage)

for infection-related workup; all-cause mortality and clinical success (defined as alive and not taking a BSAF). The latter two outcomes were assessed at 6 weeks after the end of the episode or at day –1 before subsequent chemotherapy.

Data Analysis

Baseline characteristics are described using measures of central tendency. The primary outcome of adherence was determined for post-implementation episodes overall and for the underlying diagnosis of allo-HSCT, AML, or ALL. Adherence in the post-implementation phase was also assessed for the subgroup of first episodes. A "first episode" referred to a patient not having received chemotherapy in the 6-month period before the start of the episode being assessed.

Secondary outcomes were compared for all the pre- and post-implementation episodes and for the fully adherent subgroup. In addition, a sensitivity analysis restricted to first episodes compared secondary outcomes for the pre- and post-implementation phases.

Comparisons of dichotomous variables used the chi-square or Fisher exact test; the independent t-test or Mann–Whitney test was used for continuous variables as appropriate. A p value less than 0.05 was considered significant. Statistical analyses were performed using the IBM SPSS Statistics software application (version 24.0 for Windows: IBM, Armonk, NY, U.S.A.).

RESULTS

Patient Population

Of 182 episodes consecutively screened for enrolment, 146 (80%) met the eligibility criteria, and 6 were excluded (Figure 1). Overall, 140 episodes involving 102 patients were included. Of those 140 episodes, 70 were in the pre-implementation phase (May 2012 to September 2013). The remaining 70 were in the post-implementation phase (February 2014 to June 2015).

Descriptive characteristics of episodes in the pre- and post-implementation phases were similar, including the mean duration of study enrolment and of the episode (Table I). The reasons for an episode reaching its end were white cell count recovery (125/140, 89.3%), discharge (10/140, 7.1%), next chemotherapy cycle (3/140, 2.1%), and death (2/140, 1.4%), a distribution that was not significantly different between the phases ($p = 0.172$). Antifungal prophylaxis with fluconazole was used in more than 90% of episodes in each phase. Anti-mold prophylaxis with posaconazole was not prescribed for any episode.

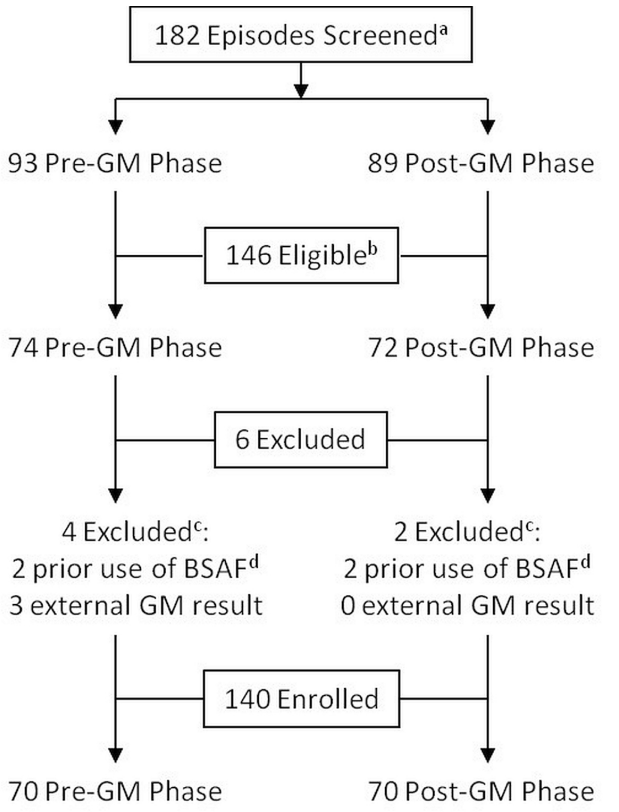

FIGURE 1 Schematic of the study's screening, eligibility, and enrolment process. [a]Based on chemotherapy protocol. [b]Based on hematologic diagnosis (matched related allogeneic hematopoietic stem-cell transplantation, or acute myeloid or lymphoid leukemia). [c]Individual episodes could have met more than 1 criterion for exclusion. [d]Broad-spectrum antifungal [BSAF (amphotericin B deoxycholate or lipid, caspofungin, or voriconazole)] administered for 3 or more consecutive days during the week before the start of the episode. GM = galactomannan.

Study Outcomes

Primary Outcome

Adherence to the GM screening protocol was observed in 61 of the 70 post-implementation episodes (87%), with 40 episodes (57%) being fully adherent and 21 (30%) being partially adherent. Nonadherence was observed in 9 episodes (13%) because no GM screens were performed. Full adherence was significantly greater for episodes involving allo-HSCT than for those involving AML or ALL: 11/12 (92%), 24/46 (52%), and 5/12 (42%) respectively ($p = 0.024$). For the sub-analysis of first episodes, adherence was observed in 43 of 50 episodes (86%), with 26 episodes (52%) being fully adherent. Full adherence for first episodes by diagnosis tended to be higher for those involving allo-HSCT (7/8, 87.5%) than for those involving AML (16/34, 47%) or ALL (3/8, 37.5%), $p = 0.080$.

Secondary Outcomes

Table II shows the data for secondary outcomes. Receipt of BSAFs was significantly more common in pre-implementation episodes than in post-implementation episodes (27% vs. 7%, $p = 0.002$). However, the mean time to BSAF initiation and the mean duration of therapy were similar in both phases. For all episodes receiving BSAFs, voriconazole was most commonly prescribed (16/24), followed by caspofungin (8/24). The most common indication for the use of BSAFs was persistent fever (11/19) in the pre-implementation episodes and diagnostic imaging (3/5) in the post-implementation episodes. At least 1 complication attributed to BSAFs was documented in 8 of 19 pre-implementation episodes and in 1 of 5 post-implementation episodes. Compared with post-implementation episodes, significantly more pre-implementation episodes involved

TABLE I Characteristics of episodes relative to implementation of the galactomannan screening protocol

Characteristic	Before screening	After screening			
		All episodes	*p* Value	Full-adherence episodes	*p* Value
Episodes assessed (*n*)	70	70		40	
Mean age (years)	56.3±13.2	55.1±13.6	0.593	54.0±12.4	0.375
Sex [*n* (%) men]	34 (49)	40 (57)	0.310	20 (50)	0.885
Diagnosis [*n* (%)]			0.576		0.100
AML	51 (73)	46 (66)		24 (60)	
ALL	11 (16)	12 (17)		5 (13)	
Allo-HSCT	8 (11)	12 (17)		11 (28)	
First episodes[a] [*n* (%)]	52 (74)	50 (71)	0.704	26 (65)	0.302
Neutropenia[b]					
Occurrence [*n* (%)]	70 (100)	70 (100)	NA	40 (100)	NA
Mean duration (days)	17.9±8.0	18.3±8.0	0.750	16.5±7.3	0.360
Mean duration (days)					
Of study enrolment	57.1±15.5	59.8±16.2	0.315	58.8±16.4	0.589
Of episodes	22.7±7.6	23.0±7.9	0.802	20.9±6.5	0.211
Fluconazole prophylaxis [*n* (%)]	64 (91)	67 (96)	0.301	38 (95)	0.488
Broad-spectrum antibiotics[c] [*n* (%)]	66 (94)	68 (97)	0.404	39 (98)	0.436

[a] Patients not having received chemotherapy for 6 or more months.
[b] Absolute neutrophil count less than 0.5×10^9/L, or if neutrophil count not available, total peripheral leucocyte count less than 1×10^9/L.
[c] Ceftazidime, ciprofloxacin, imipenem, meropenem, or piperacillin–tazobactam for 3 or more consecutive days.
AML = acute myeloid leukemia; ALL = acute lymphoid leukemia; Allo-HSCT = matched related allogeneic hematopoietic stem-cell transplantation; NA = not applicable.

at least 1 consultation (46% vs. 26%, $p = 0.014$), primarily with the Infectious Diseases service. Although more episodes in the pre-implementation phase involved diagnostics (computed tomography imaging or bronchoalveolar lavage), the difference between phases was nonsignificant.

All-cause mortality was available for the 140 enrolled episodes, and it was not significantly different between the phases. However, clinical success at the final assessment was observed in significantly fewer pre-implementation episodes than in post-implementation episodes (79% vs. 98%, $p < 0.001$). Findings in the subgroup of fully adherent post-implementation episodes demonstrated significance similar to that seen in the overall population, with the additional observation that significantly fewer episodes involved diagnostics.

A sensitivity analysis restricted to first episodes showed no significant differences in baseline characteristics. Significantly more pre-implementation episodes involved receipt of BSAFs and consultations (mainly with the Infectious Diseases service), and significantly fewer showed clinical success, but with no difference in all-cause mortality (Tables III and IV).

DISCUSSION

Adult hematology inpatients with neutropenia at high risk of IFD and receiving fluconazole prophylaxis are the population identified by the Infectious Diseases Society of America as those for whom serial serum GM screening is most likely to be a useful adjunctive test in the diagnosis of aspergillosis[14]. At our centre, a GM screening protocol was implemented to optimize BSAF use. The present study assesses clinician adherence to the GM screening protocol and compares patient outcomes and the use of BSAFs and selected resources before and after implementation of the GM protocol.

Our results show that adherence to the GM screening protocol was observed in most post-implementation episodes (87%). We also found favourable results for the secondary outcomes studied, including fewer episodes involving receipt of BSAFs, consultations, and diagnostics after implementation of the GM screening protocol. Moreover, despite the decreased use of those resources, significantly more episodes in the post-implementation phase showed clinical success at the final assessment, but with no difference in all-cause mortality.

We observed that full adherence to the protocol was significantly greater for episodes of allo-HSCT than for those of induction chemotherapy for acute leukemia. We speculate that the higher adherence rate in allo-HSCT episodes is related to those admissions being elective, with their day-to-day management being overseen by a consistent team, which is a situation different than that for the acute leukemia patients.

Prospective trials investigating the incorporation of GM as the sole non-culture-based marker into a pre-emptive diagnostic-driven strategy have examined the use of BSAFs as a key outcome and have reported reductions ranging

TABLE II Secondary outcomes for episodes relative to implementation of the galactomannan screening protocol

Outcome	Before screening	After screening			
		All episodes	*p* Value[a]	Full-adherence episodes	*p* Value[a]
Episodes assessed (*n*)	70	70		40	
Broad-spectrum antifungals[b]					
Used [*n* (%)]	19 (27)	5 (7)	**0.002**	0 (0)	**<0.001**
Mean time to start (days)	15.1±7.0	14.2±7.2	0.800	NA	NA
Mean duration of therapy (days)	10.3±5.4	9.0±3.2	0.610	NA	NA
Consultations during an episode [*n* (%)]					
≥1 With infectious diseases or respirology	32 (46)	18 (26)	**0.014**	8 (20)	**0.007**
With infectious diseases	30 (43)	16 (23)	**0.012**	6 (15)	**0.003**
With respirology	12 (17)	6 (9)	0.130	2 (5)	0.066
Diagnostics during an episode [*n* (%)]					
≥1 CT or BAL	32 (46)	22 (31)	0.083	10 (25)	**0.032**
≥1 CT	30 (43)	22 (31)	0.162	10 (25)	0.061
≥1 BAL	8 (11)	3 (4)	0.116	1 (3)	0.151
Outcomes [*n* (%)]					
All-cause mortality[c]	8 (11)	4 (6)	0.366	2 (5)	0.322
Clinical success[d]	49 (79) (62 episodes)	65 (98) (66 episodes)	**<0.001**	38 (100) (38 episodes)	**0.002**

[a] Significant values shown in boldface type.
[b] Amphotericin B deoxycholate or lipid, caspofungin, or voriconazole.
[c] Death from any cause, assessed at 6 weeks after the end of the episode or at day –1 before subsequent chemotherapy.
[d] Alive and not taking a broad-spectrum antifungal, assessed at 6 weeks after the end of the episode, or at day –1 before subsequent chemotherapy.
NA = not applicable; CT = computed tomography; BAL = bronchoalveolar lavage.

from 11% to 27%[1,9,13]. In our study, episodes involving receipt of BSAFs declined by 20% after implementation of the GM screening protocol. In addition, significantly fewer episodes involved consultations by the Infectious Diseases or Respirology service for infection-related workups. Importantly, those results were sustained in a sensitivity analysis restricted to first episodes (that is, patients who had not received chemotherapy for at least 6 months).

Although our study was not designed to determine the reasons for changes in the use of resources in the post-implementation phase, it is possible that serial negative GM results in a persistently febrile patient who was otherwise clinically well might have increased the clinician's comfort in deferring BSAFs, consultations, or additional diagnostics. The GM test is known to have a high negative predictive value in high-risk hematology patients when disease prevalence is low[15]. The assessment of patient outcomes is of particular importance, given the reductions observed in the use of BSAFs and resources after implementation of the GM screening protocol. Mortality has been assessed at various time points in prospective studies incorporating GM diagnostic testing, with reported rates of approximately 5%–18%[1,9,13]. We chose to assess patient outcomes at 6 weeks after the end of the episode because that period most closely approximates time to mortality from invasive aspergillosis; longer periods might reflect death from confounding causes[16,17]. The all-cause mortality was 2% for first episodes, which represented individual patients, and 6% for all episodes after implementation of the GM screening protocol. Our observations of a lack of significant difference in all-cause mortality and significantly more episodes showing clinical success at the final assessment after GM protocol implementation suggests that patients were safely left without treatment. In addition, fewer episodes involved antifungal-related complications.

The limitations of our study include its retrospective design and small sample size (given our available resources). Despite the design, a complete dataset was available for all episodes enrolled. In addition, efforts were made to ensure accuracy by piloting the data collection tool before study initiation and by incorporating an independent data audit for 10% of episodes. Although the sample size is small, significant differences were observed for the use of BSAFs and consultation services, and for the number of episodes showing clinical success at final assessment. Importantly, the significant differences observed for the overall study population remained consistent for the subgroups of fully adherent post-implementation episodes and first episodes. Although changes in concurrent practices over the study period might have contributed to the favourable differences between phases, the treating hematologists and the chemotherapy protocols used remained consistent over the 36-month study period. In addition, decisions about the use of BSAFs, consultations, and diagnostics were at the discretion of clinicians in both study phases.

The GM screening protocol in high-risk patients receiving fluconazole prophylaxis has been in use at our centre

TABLE III Characteristics of first episodes relative to implementation of the galactomannan screening protocol

Characteristic	Implementation of screening		*p* Value
	Before	After	
Episodes assessed (*n*)	52	50	
Mean patient age (years)	55.5±14.1	55.0±14.5	0.882
Sex [*n* (%) men]	23 (44)	28 (56)	0.235
Diagnosis [*n* (%)]			0.428
AML	39 (75)	34 (68)	
ALL	9 (17)	8 (16)	
Allo-HSCT	4 (8)	8 (16)	
Neutropenia[a]			
Occurrence [*n* (%)]	52 (100)	50 (100)	NA
Mean duration (days)	18.8±8.6	19.3±8.1	0.760
Mean duration (days)			
Of study enrolment	57.0±17.2	61.1±17.0	0.158
Of episodes	23.6±8.0	24.3±8.2	0.688
Fluconazole prophylaxis [*n* (%)]	47 (90)	49 (98)	0.102
Broad-spectrum antibiotics[b] [*n* (%)]	49 (94)	48 (96)	0.679

[a] Absolute neutrophil count less than 0.5×10^9/L, or if neutrophil count not available, total peripheral leucocyte count less than 1×10^9/L.
[b] Ceftazidime, ciprofloxacin, imipenem, meropenem, or piperacillin–tazobactam for 3 or more consecutive days.
AML = acute myeloid leukemia; ALL = acute lymphoid leukemia; Allo-HSCT = matched related allogeneic hematopoietic stem-cell transplantation; NA = not applicable.

TABLE IV Secondary outcomes for first episodes relative to implementation of the galactomannan screening protocol

Outcome	Implementation of screening		*p* Value[a]
	Before	After	
Episodes assessed (*n*)	52	50	
Broad-spectrum antifungals[b]			
Used [*n* (%)]	12 (23)	4 (8)	**0.036**
Mean time to start (days)	17.0±4.8	15.5±7.6	0.644
Mean duration of therapy (days)	9.9±4.3	10.0±2.6	0.971
Consultations during an episode [*n* (%)]			
≥1 With infectious diseases or respirology	22 (42)	10 (20)	**0.015**
With infectious diseases	20 (38)	9 (18)	**0.022**
With respirology	9 (17)	5 (10)	0.284
Diagnostics during an episode [*n* (%)]			
≥1 CT or BAL	21 (40)	17 (34)	0.505
≥1 CT	20 (38)	17 (34)	0.639
≥1 BAL	6 (12)	3 (6)	0.488
Outcomes [*n* (%)]			
All-cause mortality[c]	4 (8)	1 (2)	0.363
Clinical success[d]	40 (83) (48 eps)	48 (98) (49 eps)	**0.016**

[a] Significant values shown in boldface type.
[b] Amphotericin B deoxycholate or lipid, caspofungin, or voriconazole.
[c] Death from any cause, assessed at 6 weeks after the end of the episode or at day –1 before subsequent chemotherapy.
[d] Alive and not taking a broad-spectrum antifungal, assessed at 6 weeks after the end of the episode or at day –1 before subsequent chemotherapy.
CT = computed tomography; BAL = bronchoalveolar lavage; eps = episodes.

for nearly 4 years. Our practice is evolving based on continuous monitoring of the local epidemiology of IFD and on changes in patterns of antifungal use for prophylaxis[18,19].

CONCLUSIONS

This retrospective cohort study found that adherence to a GM screening protocol was 87% and was significantly greater for the allo-HSCT population than for acute leukemia populations. Implementation of a GM screening protocol in high-risk hematology inpatients with neutropenia and receiving fluconazole prophylaxis was feasible and was associated with significantly fewer episodes involving receipt of BSAFS and consultations and significantly more episodes showing clinical success. Those results support current Infectious Diseases Society of America recommendations[14].

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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