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ORIGINAL ARTICLE

Usefulness of serum galactomannan in initiating and modifying antifungal therapy in children with cancer and persistent high-risk febrile neutropenia

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Summary

Background: Invasive fungal disease is a major cause of morbidity and mortality in children with cancer and high-risk febrile neutropenia (HRFN). Repeated serum galactomannan (sGM) measurements have been described as an effective tool to guide therapy in adults under suspicion of invasive aspergillosis. However, the utility of this approach has not been reported in paediatric population.

Objectives: To evaluate the usefulness of sGM measurements in initiating and modifying antifungal therapy (AFT) in children with cancer and persistent HRFN.

Patients/Methods: Nested case-control study in children with cancer and persistent HRFN episodes, between July 2013 and January 2019. Patients were classified as cases and controls depending on if they received AFT or not, respectively. Through odds ratio analysis, we assessed the role of sGM positivity in the AFT initiation decision. Then, we analysed the group of patients that initiated AFT, and compared those who had AFT modifications and those who did not, analysing different sGM kinetics thresholds.

Results: A total of 191 episodes from children with persistent HRFN were enrolled, of which 107 received AFT and 84 did not. The median age was 7 years (IQR 4-12), 52% were male and 89% had a haematologic malignancy as underlying disease. Positive sGM was not associated with AFT initiation (OR 0.99, 95% CI 0.43-2.33, P = .99). A difference threshold in sGM $\Delta \geq 0.3$ sGM was significantly associated with AFT modification (OR 5.07, 95% CI 1.02- 25.70, P = .04).

Conclusions: Our results suggest the utility of serial sGM sampling during AFT in children with persistent HRFN.

KEYWORDS

antifungal agents, aspergillosis, chemotherapy-induced febrile neutropenia, febrile neutropenia in children, galactomannan, infectious diseases, invasive fungal infections, paediatric oncology, paediatrics

1 | INTRODUCTION

Cancer represents a major cause of death for children and adolescents, with global estimates of ~300 000 new diagnosis per year,[1] and survival rates varying between low- to-middle-income countries and high-income countries.[2] In Chile, the reported incidence is ~14 cases per 100 000 children under the age of 15, with a median of 467 new cases per year and an all-cancer 5-year survival rate of 75%-79%,[3] similar to survival rates documented in high-income countries.[4]

Despite improvements in childhood cancer outcomes,[4] major immuno-toxic side effects because of aggressive chemotherapy are frequent, with febrile neutropenia (FN) being one of the main causes of morbidity and mortality in paediatric oncologic population.[5,6]

Among infections, invasive fungal diseases (IFD) are relevant because of high morbidity and mortality rates.[7] In Chile, evidence suggests that 5.8% of episodes of FN have a final diagnosis of probable/proven IFD,[8] according to European Organization for Research and Treatment of Cancer (EORTC)/ Mycoses Study Group criteria,[9,10] and that mortality is up to 10 times higher within this group.[8] *Candida* species and *Aspergillus* species are the most common causes of IFD, with invasive aspergillosis (IA) being responsible of the most severe cases,[11] and having a wide range of prevalence (0.5%-30.8%)[12,13] documented in literature depending on the population and diagnostic definition used in each report.

Early diagnosis and antifungal therapy (AFT) are considered to be the most important factors influencing survival in IFD, but a rational approach to AFT use remains difficult through conventional culture, histology or imaging methods.[7,8,14] To tackle this problem in children with cancer, our group recently examined a pre-emptive AFT initiation strategy over an empirical AFT strategy, reporting similar efficacy and clinical outcome with reduced AFT overuse in the pre-emptive group,[15] and encouraging a more meticulous examination of pre-emptive grouping factors.

Galactomannan (GM) is a polysaccharide consisting of a mannose backbone and a variable number of galactofuran side chains,[16,17] and makes up a major part of the cell wall of *Aspergillus* spp.[17] In recent years, detection of serum galactomannan (sGM) antigen has become widely available and accepted as a diagnostic tool for IA,[5,7,14] with baseline sGM and GM kinetics being strongly associated with survival in IA.[16,18]

In immunocompromised adults, an early reduction during the first 2 weeks of AFT in sGM has been associated with a higher probability of satisfactory response to therapy,[18-21] suggesting a clinical response utility in serial sGM measurements. In paediatric population, its sensitivity and specificity for IFD diagnosis has been explored by multiple studies, with varying results depending on the definition used.[12,22,23] Nonetheless, the predictive role of sGM and its kinetics in paediatric oncology high-risk FN (HRFN) population and specific thresholds suggesting therapy effectiveness/failure, along with comprehensive rationales for on-the-go clinical decisions, are still lacking.[16,22,23]

The aim of this study was to evaluate the usefulness of sGM measurements in initiating and modifying AFT in children with cancer and persistent HRFN.

2 | PATIENTS AND METHODS

2.1 | Study design and patients

Nested case-control study in children with cancer and persistent HRFN episodes. Data were collected between July 2013 and January 2019 from paediatric patients in the oncology units of six hospitals in Santiago, Chile, that belong to the National Child Program of Antineoplastic Drugs network (PINDA) and were analysed retrospectively. Children and adolescents with cancer, ≤18 years of age, admitted because of a FN episode were invited to participate and enrolled after parental and child informed consent or assent (when older than 8 years of age). The study was approved by the Ethics Committee of each participating institution. Inclusion criteria considered data from HRFN episodes of children with at least one sGM measurement during follow-up. Exclusion criteria were pre-existing treatment or prophylaxis with voriconazole or posaconazole at admission.

Each child with an episode of FN was classified at admission as having low-risk febrile neutropenia (LRFN) or HRFN based on the stratification risk-score of Santolaya et al.[24] After the initial evaluation, children were treated according to the guidelines for the management of FN in children with cancer.[25,26] All children with HRFN who continued with fever and neutropenia at day 4 of antimicrobial treatment were considered having a persistent HRFN and were evaluated with a standardised clinical, laboratory, imaging and microbiological panel for IFD. The evaluation included a blood panel with absolute neutrophil count (ANC), absolute monocyte count (AMC), C-reactive protein (CRP), blood cultures and sGM; imaging through chest CT scan and abdominal ultrasound; and other diagnostic evaluations according to clinical presentation (sinus CT scan, fundoscopy, echocardiography, MRI, bronchoalveolar lavage, skin or other tissue biopsy). According to the protocol, all these studies were performed between day four and day six of evolution. In some cases, the imaging study was delayed due to the specific availability of each hospital. The blood panel was performed as frequently as daily depending on the clinical response of each patient.

Children with persistent HRFN episodes were evaluated daily and initiation of AFT was considered at any time of the follow-up only if persistent fever and ANC ≤ 500/mm^3 were accompanied by any of the following findings suggesting IFD: (a) clinical/imaging documented pneumonia or sinusitis (characteristic chest or sinus CT scan), (b) Skin lesions suggesting IFD, (c) clinical/imaging enterocolitis, (d) unexplained CNS symptoms, (e) splenic or hepatic characteristic imaging, (f) positive sGM and (g) positive mycological finding.

Antifungal agents included polyenes (liposomal amphotericin B, lipidic amphotericin B), echinocandins (micafungin, caspofungin,

anidulafungin) and triazoles (fluconazole, voriconazole, posaconazole), selected according to clinical, imaging and laboratory findings and antifungal prophylaxis records. AFT was initiated, modified or stopped according to clinical, laboratory, imaging and microbiological findings in each individual case, according to each clinical team's decisions. Day of initiation of AFT and further modifications during follow-up were recorded accordingly. Patients were monitored until day 30 of follow-up for clinical, laboratory, imaging and microbiological resolution. Episodes were reviewed by our local Paediatric Oncology/Infectious Disease Board of Experts, who defined the final diagnosis of proven, probable, possible or absence of IFD.

Our Paediatric Oncology/Infectious Diseases board of experts classified patients receiving AFT into three groups, according to the recommendation of the literature regarding the coverage of different antifungals against IA[26,27]: Group (1) patients that did not receive AFT or received fluconazole; Group (2) patients that received lipidic amphotericin B or echinocandins; and Group (3) patients that received liposomal amphotericin B or voriconazole.

Through odds ratio (OR) analysis, we assessed the performance of sGM in two scenarios. In our first analysis, we calculated the OR of a positive sGM as a predictor of AFT initiation. Data samples from all paediatric patients with persistent HRFN meeting our inclusion/exclusion criteria were considered for this analysis. Highest serum GM levels during follow-up were used as the exposure variable, considering sGM >0.5 OD as a positive exposure and sGM ≤ 0.5 OD as a negative exposure, following the literature recommended cut-off criteria.[7,16]

In our second analysis, we analysed only the group of patients that initiated AFT and divided them into those that had modifications in AFT (defined as escalation, de-escalation or adjustment) and those whose therapy remained unmodified during follow-up, and calculated the OR for different sGM kinetics as a predictor of AFT modification. In children with AFT modification, we considered the value of variation in sGM at the day of AFT modification as the exposure variable. In children with unmodified AFT, we considered absolute value of variation in sGM levels by day 14. An increase in sGM associated with AFT escalation, or a decrease in sGM associated with AFT de-escalation—representing congruent clinical relations—was considered as positive exposure. An increase in sGM associated with AFT de-escalation, or a decrease in sGM associated with AFT escalation—representing incongruent clinical relations—was considered as negative exposure. Different thresholds of sGM kinetics were analysed.

2.2 | Study definitions

(a) Neutropenia: ANC ≤ 500/mm^3; (b) Fever: single axillary temperature ≥38.5 or ≥38°C in two measurements separated by ≥1 hour; c) HRFN: a FN episode with one or more of the following risk factors at the time of admission: relapse of leukaemia as cancer type, hypotension, or quantitative CRP ≥ 90mg/L, or a FN episode with the following two factors at the time of admission: ≤7 days between the end of the last chemotherapy and the beginning of the fever and platelet count of ≤50 000/mm^3; (d) LRFN: a FN episode without the above-mentioned factors at the time of admission; (e) Persistent HRFN: fever and neutropenia ≥96 hours in a child with HRFN; (f) IFD status was defined according to the EORTC as follows: proven if the child had microbiological or histological evidence of fungal tissue invasion or a positive fungal culture obtained from a sterile site, in addition to clinical or radiological findings consistent with fungal infection; probable, the presence of one or more host factors, a clinical criterion and one or more mycological criterion by a direct test (cytology, direct microscopy or culture) or an indirect test (detection of antigen); and possible, a case meeting host factor and clinical criteria but lacking any mycological documentation[9]; (g) Cases: children with persistent HRFN that received AFT; (h) Controls**:** children with persistent HRFN that did not receive AFT; (i) Initial AFT: initial antifungal drug assigned to a patient with IFD-suggesting findings during hospitalisation; (j) Final AFT: last antifungal drug assigned to a patient during follow-up; (k) Modification of AFT was escalation: change from group 1 to group 2 or 3, and from group 2 to group 3; de-escalation: change from group 3 to group 2 or 1, and from group 2 to group 1 or adjustment: change from any AFT to another, within the same group; (l) Unmodified AFT: final AFT was the same as initial.

2.3 | Statistical analysis

2.3.1 | Sample size

Using EpiTools epidemiological program,[28] we calculated a sample size considering a confidence interval of 95% and a statistical power of 80%. For our expected OR prediction, we considered the lower end of literature reported diagnostic OR for sGM,[29] predicting an OR of at least 6% with 20% of the controls positive for the exposure variable, resulting in a sample size of at least 40 by group.

2.3.2 | Analysis considerations

We considered potential confounders in the admission characteristics of each children. Covariates were described for case and control groups separately. Categorical variables were compared using the chi-squared test. Continuous variables were compared using the Mann-Whitney test. Area-proportional Venn diagrams were constructed with Biovenn.[30]

2.3.3 | Receiver operating characteristics (ROC) analysis

We assessed our clinical congruency correction methodology through ROC analysis. The AUC of raw sGM and clinical-congruency-corrected sGM was compared. ROC continuous rating scale analysis[31] was performed on sGM kinetics difference values (sGM Δ) as predictors of

AFT modification, considering patients who had AFT modifications as true positives and those who did not as true negatives.

Statistical significance analyses were performed using MedCalc for Windows, version 15.0 (MedCalc Software). ROC significance analysis was performed with ROC analysis: web-based calculator for ROC curves (Johns Hopkins University School of Medicine).[31] A *P*-value <.05 was considered to be statistically significant. The null hypothesis was that there would be no statistically significant association of sGM between groups, or an OR ≤ 1.

3 | RESULTS

3.1 | Patient characteristics

Data from 215 episodes of children with HRFN episodes meeting the inclusion criteria were collected. Twenty four episodes were excluded: 21 episodes due to prophylaxis or pre-existing treatment with voriconazole or posaconazole and 3 episodes because of unavailable sGM measurements. A total of 191 episodes from 158 children with persistent HRFN were analysed. The median age of patients was 7 years (IQR 4-12), and 52% were male. Table 1 describes the main clinical features of children in the 191 episodes of persistent HRFN, divided for initial analysis whether an AFT was indicated (cases, N = 107) or not (controls, N = 84) during their hospitalised period. No significant differences were observed when comparing age, sex or underlying condition between groups, with haematological malignancies representing the main base disorders in both groups (92% in cases and 87% in controls, *P* = .26). Fever without a focus represented the main clinical presentation in both cases and controls (43% and 38%, respectively), with minor differences in the distribution of foci at admission. Respiratory foci were statistically different between cases and controls (21% vs 35%, *P* = .03).

TABLE 1 Characteristics from 158 children accounting for 191 episodes of persistent high-risk febrile neutropenia, divided into cases that received antifungal therapy and controls that did not, along with sGM characterisation and performance

Characteristic	Total n = 191	Cases n = 107	Controls n = 84	*P*-value
Admission clinical characterisation				
Age in years, median (IQR)	7 (4-12)	8 (4-12)	6 (4-12)	.54
Male, n (%)	100 (52)	59 (51)	41 (49)	.75
Underlying disease, n (%)				
Acute lymphocytic leukaemia	59 (31)	28 (26)	31 (37)	.10
Acute myeloid leukaemia	69 (36)	41 (38)	28 (34)	.48
Leukaemia relapse	33 (17)	21 (20)	12 (14)	.28
Solid tumour	20 (11)	9 (8)	11 (13)	.26
Other neoplasms[a]	10 (5)	8 (8)	2 (2)	.07
Use of GSF, n (%)	54 (28)	29 (27)	25 (30)	.68
Use of CVC, n (%)	174 (91)	98 (91)	76 (90)	.79
Clinically identified fever source, n (%)				
Fever without a focus	78 (41)	46 (43)	32 (38)	.49
Respiratory foci	51 (27)	22 (21)	29 (35)	.03
Gastrointestinal foci	45 (23)	28 (26)	17 (20)	.32
Other foci[b]	17 (9)	11 (10)	6 (7)	.44
sGM performance OR 0.99, CI 0.43-2.33 (P=.99)				
Patients with positive sGM, n (%)	25 (13)	14 (13)	11 (13)	1.00
Follow-up sGM tests N°, median (IQR)	3 (2-3)	3 (2-4)	2 (2-3)	.41
Max sGM OD value, median (IQR)	0.80 (0.6-3.4)	1.67 (0.6-3.9)	0.67 (0.6-1.2)	.29

Abbreviations: CVC, central venous catheter; GSF, granulocyte stimulating factor.

[a]Other Neoplasm: Hodgkin's lymphoma, Non-Hodgkin's lymphoma, Bi-phenotypic/ambiguous leukaemia and infant leukaemia.

[b]Other foci: Skin/soft-tissue infection, CVC infection and urinary tract infection.

3.2 | sGM performance

A total of 25 patients had at least one positive sGM measurement during their follow-up, with no statistical differences between the cases (N = 14, 13%) and control group (N = 11, 13%), $P = 1.00$. Patients from the cases group had a median of three sGM measurements during their follow-up (IQR: 2-4). All 14 patients in this group had two or more determinations of sGM >0.5 OD (median 1.67, IQR 0.6-3.9). Patients from the control group had a median of two sGM measurements during their follow-up (IQR: 2-3). All 11 patients from the control group had only one measurement of sGM >0.5 OD (median 0.67, IQR 0.6-1.2), and AFT initiation was considered unnecessary by the local oncology/infectious diseases team in charge of them.

There was no positive nor significant association between a sGM value >0.5 OD and prescription of AFT during hospitalisation (OR 0.99, 95% CI 0.43-2.33, $P = .99$). We also analysed the OR associating sGM >0.5 OD with initiation of AFT stratifying according to underlying disease and found no significant association. We observed a non-significant trend of more AFT indicated in children with ALL/AML relapse (OR 4.7, 95% CI 0.19 to 85.43), $P = .37$.

Positive clinical, imaging and mycological findings that lead to AFT initiation are described in Figure 1. Clinical and imaging criteria accounted for 97% of the findings that lead to AFT initiation, overlapping with mycological criteria in 17% of the cases. Mycological criteria—on their own or in combination with clinical/imaging criteria—account for 24% of the findings that lead to AFT initiation, with positive sGM being the most common positive mycological criteria (42%).

3.3 | AFT population characterisation

Data from 107 persistent HRFN patients requiring AFT is summarised in Table 2, divided into 47 patients that had an AFT modification (escalation, de-escalation or adjustment) and 60 patients with unmodified AFT during follow-up. Significant clinical differences are shown when comparing both groups. Children with modified AFT reported worst outcome in mortality at day 30, more days of hospitalisation, more days of fever and more requirement of intensive care unit (ICU) ($P < .05$). Day of AFT initiation showed no statistical differences between groups ($P = .60$). The modified AFT group required significantly higher days of AFT during hospitalisation vs the unmodified AFT group (median 14 days vs 9 days, respectively, $P < .0001$). Diagnosis of probable IFD was significantly higher in children belonging to the group that modified their AFT, in contrast to the diagnosis of absence of IFD, which was significantly higher in children in whom their AFT was not modified. Maximun value of sGM during the follow-up was similar in children on which AFT was modified or was not modified (Median of 1.88 OD versus 0.69 OD, $P = .35$).

Antifungal therapy modifications were further characterised in the 47 patients who had modifications, detailing escalations, de-escalations and adjustments as per previously provided definitions, according to the final IFD diagnosis for each case (Table 3). The most frequent escalation was from echinocandin to liposomal amphotericin B, and the most frequent de-escalation was from echinocandin to fluconazole.

Demographic, clinical, imaging and mycological findings for 19 children with proven and probable IFD are detailed in Table 4,

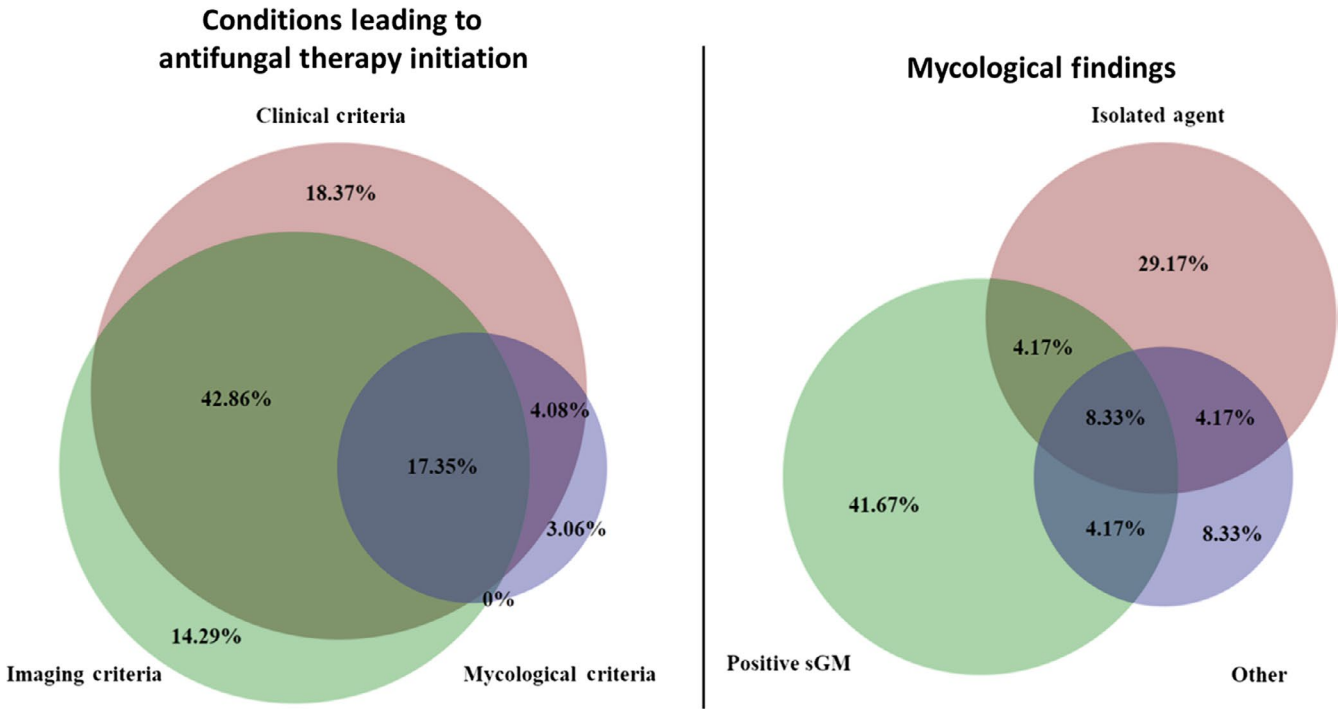

FIGURE 1 Area-proportional Venn diagram illustrating clinical, imaging and mycological criteria for antifungal therapy initiation. On the left, conditions leading to antifungal therapy initiation are diagrammed; on the right, mycological criteria are further divided according to the positive finding

TABLE 2 Clinical outcome, final invasive fungal disease diagnosis and sGM characterisation and performance of children with persistent high-risk febrile neutropenia that received antifungal therapy, divided into patients with and without antifungal therapy modification

Characteristic	Modified antifungal therapy n = 47	Unmodified antifungal therapy n = 60	*P*-value
Clinical outcome			
Mortality at day 30, n (%)	6 (13)	1 (2)	.02
Days of hospitalisation, median (IQR)	25 (15-34)	17 (14-23)	.01
Days of fever, median (IQR)	14 (7-23)	8 (6-15)	.01
Need of ICU, n (%)	15 (32)	8 (13)	.02
Day of AFT initiation, median (IQR)	8 (6-11)	7 (5-10)	.60
Days of AFT received during hospitalisation, median (IQR)	14 (9-23)	9 (7-11)	<.0001
EORTC invasive fungal disease final diagnosis			
Proven, n (%)	6 (13)	5 (8)	.39
Probable, n (%)	7 (15)	1 (2)	.01
Possible, n (%)	20 (42)	22 (37)	.60
No IFD, n (%)	14 (30)	32 (53)	.01
sGM performance			
Positive sGM, n (%)	9 (19)	5 (8)	.09
Follow-up sGM tests N°, median (IQR)	3 (2-4)	2 (2-3)	.04
Max sGM OD value, median (IQR)	1.88 (0.7-4.8)	0.69 (0.6-3.1)	.35

including maximum sGM and BAL GM during follow-up, isolated mycological agent and clinical outcome for each individual case. Seventeen/nineteen patients with proven/probable IFD had a haematological malignancy, specially AML (8 cases) and relapse of leukaemia (5 cases). Of eleven children with proven IFD, nine had invasive candidiasis. Of eight children with probable IFD, all of them had pneumonia and GM, in serum or in BAL, over the respective cut-off value.

3.4 | sGM Δ performance

We assessed our clinical congruency correction using ROC analysis, concluding there was a significant increase in the AUC of corrected sGM values when compared against the reference, while the AUC of raw sGM values was not significant against the reference for determining AFT modification prediction (Figure 2).

Different thresholds for sGM were analysed. There was a significant association between a sGM Δ ≥ 0.3 and AFT modification (P = .04), with an OR of 5.07 (95% CI 1.02 to 25.70). Higher thresholds display a similar trend of association, with ratios ranging from 4.24 to 7.02, albeit at the cost of significance. Lower thresholds, however, had lower OR (1.22 to 1.14) and were not significantly associated with AFT modification (P = .67 and 0.82, respectively).

We then analysed the discerning capability of the putative sGM Δ threshold ≥|0.3| in association with the prognosis of our 107 patients that received AFT. An increase in sGM Δ ≥ 0.3 was associated with a poorer prognosis, while a decrease in sGM Δ < −0.3 was associated with a better prognosis (Table 5). Significant associations were found when comparing both groups in days of hospitalisation (P = .03) and days of fever (P = .01).

4 | DISCUSSION

Quantification of sGM and its kinetics have been proposed as surrogate markers for IFD outcome and AFT response.[16] In our experience, we have found that sGM was not significantly associated with AFT initiation, implying that on its own it has unsatisfactory capability for predicting the need of AFT and requiring complementation by clinical and imaging findings. However, we have found that sGM kinetics with a variation in sGM Δ of at least 0.3 OD significantly associates to AFT modification, suggesting the utility of serial sGM sampling during the AFT period in children with persistent HRFN. We have also found that this threshold is

TABLE 3 In-depth characterisation of the 47 patients with modification of antifungal therapy during follow-up, divided into escalation, de-escalation and adjustment. Invasive fungal disease diagnosis is detailed for each antifungal therapy modification

Antifungal therapy modification characterisation	N° (total = 47)	Invasive fungal disease diagnosis			
		Proven	Probable	Possible	No IFD
Antifungal therapy escalation, n (%)	24 (51)	4 (8.5)	4 (8.5)	9 (19)	7 (15)
Fluconazole -> Echinocandin	2				2
Fluconazole -> Voriconazole	6	1		4	1
Lipidic Ampho B -> Voriconazole	5		2	3	
Echinocandin -> Liposomal Ampho B	8	3	1	1	3
Echinocandin -> Voriconazole	3		1	1	1
Antifungal therapy de-escalation, n (%)	14 (30)	1 (2)	0 (0)	6 (13)	7 (15)
Voriconazole -> Fluconazole	2				2
Voriconazole -> Echinocandin	2			1	1
Liposomal Ampho B -> Echinocandin	1	1			
Liposomal Ampho B -> Fluconazole	1			1	
Echinocandin -> Fluconazole	6			2	4
Lipidic Ampho B -> Fluconazole	2			2	
Antifungal therapy adjustment, n (%)	9 (19%)	1 (2)	3 (6)	5 (11)	0 (0)
Liposomal Ampho B -> Voriconazole	6	1	2	3	
Voriconazole -> Liposomal Ampho B	3		1	2	

Abbreviation: Ampho B, Amphotericin B.

capable of discerning two distinct groups: patients that increased sGM Δ in ≥ +0.3 OD associated with poorer prognosis and patients that decreased sGM Δ < −0.3 OD associated with better prognosis.

Limitations in our findings include the lack of a fixed amount of sGM measurements during follow-up and analysis of the optimal timing for consequent measurements; we were constrained by our data set for further refinement of our sGM Δ threshold, encouraging further studies to tackle this problem and incorporating a time dimension to sGM kinetics, as previous findings have reported different sGM Δ slopes associated with specific AFT responses and clinical outcomes.[20,32] Additionally, we did not restrict our analysis to filamentous-fungi infections only, despite sGM putative utility being limited to this group of fungus.[16,17] This was not by neglect, but by design, because our aim was to evaluate the sGM utility in the real clinical decision of initiate or not AFT in children with persistent HRFN in places where patients do not routinely receive antifungal mould prophylaxis.

Our findings are consistent with the fact that isolation of *Aspergillus* spp. (and consequent proven IFD by IA diagnosis) is exceptional, with most reported data being based on possible and probable IA diagnosis.[22,29,33] It is within this clinical uncertainty that we sought to explore sGM as a potential guide for rapid responses in the setting of usually shifting and unpredictable paediatric oncology patients.

Our findings follow a similar trend to previously reported sGM kinetics analysis in immunocompromised adult population. Chai et al[21] reported that in patients with IA and a baseline sGM >0.5, a 35% decline in sGM during the first four weeks of follow-up increased the probability of satisfactory clinical outcome, while in patients with a baseline sGM ≤0.5, every 0.1 unit increase in the sGM baseline after 2 weeks of AFT increased the likelihood of a poor clinical response by 21.6%. The same group later reported differential sGM trend profiles depending on AFT drugs utilised during a similar timeframe follow-up.[20] Neofytos et al later reported similar findings correlating sGM kinetics to clinical responses in adults.[32]

Extensive literature has also associated sGM positivity and increase during follow-up with clinical outcome,[16,18,19] adding up additional imaging and clinical criteria to further enhance the biomarker's sensitivity. Our findings continue this similar trend suggesting serial sGM measurements as a prognostic tool, although further studies

TABLE 4 Demographic, clinical, imaging and microbiological characteristics of 19 children with proven and probable IFD, including maximum sGM and BAL GM measured during follow-up and outcome

Age in years or months/ sex	Cancer type	Clinical and imaging focus	Max sGM	Max BAL GM	Microbiological findings	Outcome
Proven IFD						
11 y/female	ALL	Renal abscess	0.3		*C lusitaniae* in renal biopsy	Favourable
3 y/female	ALL	Pneumonia	0.2		BC (+) *C parapsilosis*	Favourable
1 y/male	AML	Enterocolitis	0.2		BC (+) *C albicans*	Favourable
1 y/male	AML	Central venous catheter	0.2		BC (+) *C parapsilosis*	Favourable
9 y/female	Solid tumour	No foci	0.1		BC (+) *C parapsilosis*	Favourable
5 mo/female	AML	No foci	6.7		BC (+) *C parapsilosis*	Death
8 y/male	AML	Enterocolitis	0.4		BC (+) *C albicans*	Favourable
4 y/male	ALL relapse	Enterocolitis	0.2		BC (+) *C parapsilosis*	Favourable
11 y/male	AML	Sinusitis/Pneumonia	0.5	0.5	*Rhizopus* spp. in sinus biopsy	Favourable
1 y/female	AML	Enterocolitis	0.1		BC (+) *C tropicalis*	Favourable
12 y/female	ALL relapse	Pneumonia	0.6		*A fumigatus* in lung biopsy	Favourable
Probable IFD						
18 y/female	ALL relapse	Pneumonia	0.3	1.0	-	Favourable
4 y/male	AML	Pneumonia	0.7		BC (+) CoNS	Favourable
3 y/male	Solid tumour	Pneumonia	4.1		BC (+) *Klebsiella* spp.	Favourable
17 y/male	AML relapse	Pneumonia	0.7		-	Favourable
9 y/female	ALL	Pneumonia	0.2	0.8	-	Favourable
14 y/female	AML	Pneumonia	1.9	4.1	-	Favourable
11 y/male	ALL relapse	Sinusitis/Pneumonia	4.8	0.2	BC (+) *E coli*	Death
5 y/male	ALL	Pneumonia	1.5	0.2	-	Favourable

Abbreviations: ALL, acute lymphocytic leukaemia; AML, acute myeloid leukaemia; BAL, bronchoalveolar lavage; BC, blood culture; CoNS, coagulase-negative *Staphylococcus;* CT, computed tomography.

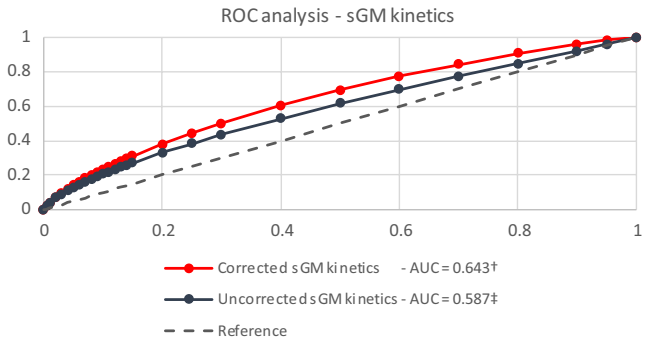

FIGURE 2 Receiver operating characteristic analysis comparing raw serum galactomannan kinetics and corrected serum galactomannan kinetics

TABLE 5 Discerning capability of an sGM Δ threshold ≥|0.3| in predicting clinical outcome of 107 children that received antifungal therapy

Clinical outcome	Δ ≥ +0.3	Δ < −0.3	*P*-value
Mortality at day 30, n (%)	2 (40)	0 (0)	.13
Days of hospitalisation, median (IQR)	30 (26-47)	16 (15-21)	.03
Days of fever, median (IQR)	25 (21-35)	8 (7-11)	.01
Need of ICU, n (%)	4 (80)	2 (40)	.22
Days of AFT, median (IQR)	16 (13-40)	12 (7-13)	.09

Abbreviations: AFT, antifungal therapy; ICU, intensive care unit.

with appropriate potency design should be performed before categorically reaching this conclusion in paediatric population.

With our findings, we suggest that sGM kinetics during follow-up has potential not only as an outcome predictor, but also as a clinical decisions guide. Our main novelty lies within the clinical congruence analysis exerted upon our data, and we encourage further studies to analyse the subject with a similar approach. This was not a study evaluating in a prospective way whether sGM has a benefit of guiding therapy. Although data suggest that changing therapy according

to sGM could be beneficial. A prospective validation will be required before fully gauging our findings' extensive use, with strict protocols in sGM measurements during hospitalisation follow-up to counter our possible omitted-variable bias inherent to retrospective design weaknesses.

In conclusion, we have shown that in our experience, sGM measurement was not a good predictor for the onset of AFT in children with persistent HRFN. However, its kinetics can be used to encourage a rapid clinical response and AFT modification, and could be related to clinical outcome in paediatric oncology population. The early identification of patients at risk for therapy failure is crucial for prompt clinical interventions, similar to the early identification of patients where it is possible to carry out an active stewardship of AFT. An active monitoring cemented on top of optimal laboratory support is essential for optimising management in this group of patients, and we encourage further evidence-based refinements to this approach.

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CONFLICTS OF INTERESTS

None to declare.

AUTHOR CONTRIBUTION

Matías Delgado: Conceptualization (lead); Data curation (equal); Formal analysis (lead); Investigation (equal); Methodology (lead); Validation (lead); Writing-original draft (lead); Writing-review & editing (lead). **Romina Valenzuela:** Data curation (equal); Formal analysis (equal); Investigation (equal); Project administration (equal); Supervision (equal). **Verónica De la Maza:** Data curation (equal); Formal analysis (equal); Investigation (equal); Project administration (equal); Resources (equal); Supervision (equal). **Marcela Rabello:** Conceptualization (equal); Formal analysis (equal); Methodology (equal); Validation (equal); Writing-original draft (equal). **Ana María Alvarez:** Formal analysis (equal); Investigation (equal); Methodology (equal); Supervision (equal). **Verónica Contardo:** Data curation (equal); Formal analysis (equal); Project administration (equal); Supervision (equal); Writing-review & editing (equal). **Marcela Zubieta:** Data curation (equal); Formal analysis (equal); Investigation (equal); Validation (equal); Writing-review & editing (equal). **Valentina Gutierrez:** Data curation (equal); Methodology (equal); Writing-review & editing (equal). **Ximena Claverie:** Data curation (equal); Formal analysis (equal); Investigation (equal); Validation (equal); Writing-review & editing (equal). **Juan Pablo Torres:** Conceptualization (lead); Formal analysis (lead); Methodology (equal); Resources (equal); Writing-original draft (equal); Writing-review & editing (equal). **Carmen Salgado:** Formal analysis (equal); Investigation (equal); Project administration (equal); Validation (equal); Writing-review & editing (equal). **Monica Varas:** Investigation (equal); Supervision (equal); Writing-review & editing (equal). **Carmen Avilés:** Investigation (equal); Resources (equal); Validation (equal). **Juan Tordecilla:** Data curation (equal); Formal analysis (equal); Methodology (equal); Visualization (equal); Writing-review & editing (equal). **Marcela Venegas:** Investigation (equal); Resources (equal); Writing-review & editing (equal). **Milena Villarroel:** Formal analysis (equal); Investigation (equal); Methodology (equal); Resources (equal). **Maria Santolaya:** Conceptualization (lead); Formal analysis (lead); Funding acquisition (lead); Project administration (lead); Writing-original draft (lead); Writing-review & editing (lead).

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