Risk Factors Associated With Invasive Fungal Disease in Children With Cancer and Febrile Neutropenia

A Prospective Multicenter Evaluation

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Background: Empiric antifungal treatment has become standard of care in children with cancer and prolonged fever and febrile neutropenia (FN), with the downside that it leads to significant over treatment. We characterized epidemiologic, clinical, and laboratory features of invasive fungal disease (IFD) in children with cancer and FN with the aim to identify risk factors for IFD that can aid in better selecting children who require antifungal treatment.

Methods: In a prospective, multicenter study, children admitted with FN at high-risk for sepsis, in 6 hospitals in Santiago, Chile were monitored from admission until the end of the FN episode. Monitoring included periodic evaluation of clinical findings, absolute neutrophil count, absolute monocyte count (AMC), serum C-reactive protein (CRP), bacterial cultures, imaging studies, and galactomannan antigen. A diagnosis of proven, probable, and possible IFD was made after episode resolution based on European Organization for Research and Treatment of Cancer classification.

Results: A total of 646 high-risk FN episodes were admitted during the study period, of which 604 were enrolled. IFD was diagnosed in 35 episodes (5.8%) of which 7 (1.2%) were proven, 10 (1.6%) probable, and 18 (3.0%) possible. Four variables obtained on day 4 were significantly more common in IFD cases, which were presence of fever, absolute neutrophil count $\leq$500/mm^3, AMC $\leq$100/mm^3, and CRP $\geq$90 mg/L. The combination of fever, AMC $\leq$100/mm^3, and CRP $\geq$90 at day 4 provided a RR for IFD of 5.4 (99% CI, 3.2–9.2) with a sensitivity of 75%, specificity of 87%, positive and negative predictive values of 13% and 99%, respectively.

Conclusions: Fever persisting at day 4 of admission, together with AMC $\leq$100 and CRP $\geq$90 significantly increased the risk for IFD in children with cancer.

Key Words: invasive fungal disease, febrile neutropenia, risk factors

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The incidence of invasive fungal disease (IFD) has increased in pediatric cancer patients during the last decade as a consequence of more aggressive chemotherapies and anti-infective strategies implemented with the aim to increase patient survival.[1,2] Prolonged neutropenia, severe mucositis, use of broad-spectrum antibiotics, steroids, and invasive procedures contribute to this increase.[3] In this scenario, a rationale approach for diagnosis and management of IFD is required to curtail their potential negative impact in morbidity and mortality.

Candida and Aspergillus species are the most frequent fungal pathogens, causing IFD in children with febrile neutropenia (FN).[4,5] Invasive candidiasis is associated with the second highest case fatality rate reaching approximately 10%.[6,7] The overall risk of death in patients with invasive aspergillosis can reach 30% to 50%.[8,9] Early diagnosis of IFD and prompt implementation of aggressive antifungal treatment has proved to be critical for patient survival.[10,11] Unfortunately, early identification of the etiologic pathogen causing an IFD is extremely difficult in children. Fungal cultures lack sensitivity, histologic diagnosis require invasive procedures,[2,12] imaging studies lack specificity,[13] galactomannan (GM) antigen detection has a relatively low sensitivity in children compared with adults,[14–16] and fungal deoxyribonucleic acid detection, although promising, has not been fully validated in this population.[17–19]

Current recommendations propose to begin empiric antifungal therapy at day 5 of fever in children with severe chemotherapy-associated neutropenia receiving appropriate antibacterial treatment.[20] The problem with this approach is the over treatment of children meeting the above criteria but who do not have an IFD that could lead to an increase in adverse events, prolonged hospitalizations, and elevated costs associated with the use of antifungal drugs.[21]

Studies describing the epidemiology, clinical and laboratory characteristics of IFD have been performed, albeit mostly in adult populations.[22,23] In children, studies have focused on IFD incidence in different populations with results that range from 6.9% in Japan to 13.6% in Turkey.[24,25] We have previously described that 6% of FN episodes in children with cancer and FN were consistent with proven or probable IFD.[26] More recently, Castagnola et al prospectively described clinical features and outcome in a large series of 96 episodes of IFD in Italian children.[3] Nevertheless, studies on the identification of risk factors for IFD in children with cancer and FN that could potentially aid in a more selective antifungal treatment strategy are scarce. In this prospective, multicenter study, our aim was to characterize epidemiological, clinical, and laboratory features of IFD and identify risk factors associated with IFD in a large population of children with cancer and FN.

METHODS

Overall Study Design and Patient Selection

We designed a prospective, multicenter study in 6 major public hospitals located in Santiago, Chile, overseen by the National Child Program of Antineoplastic Drugs. The study was conducted by physicians belonging to the Oncology and Infectious Disease Units of each hospital grouped in the National Child Program of Antineoplastic Drugs subcommittee of Infectious Diseases. The study protocol and informed consent were approved by the Ethical Committee of the National Health Ministry.

Between June 2004 and October 2006, children ≤21 years of age receiving chemotherapy for cancer required hospital admission because of a FN episode at high-risk for invasive bacterial infection (HRFN),[27,28] were invited to participate in this study. Patients undergoing hematopoietic stem-cell transplantation were excluded. Children were monitored daily until the end of the FN episode. After resolution of the FN episode, 2 investigators (M.O. and M.V.) categorized the IFD status of each episode as proven, probable, possible, or absence of 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) revised criteria.[29]

Evaluation at Admission

Patients were uniformly evaluated on the day they were admitted to the hospital with the diagnosis of FN. The study physician obtained the following information: age, gender, type of cancer, type of chemotherapy, presence of an indwelling catheter, hours of fever before admission, sign and symptom indicative of an infectious focus, temperature, arterial blood pressure, capillary refill, diagnosis of sepsis, absolute neutrophil count (ANC), absolute monocyte count (AMC), platelet count, quantitative C-reactive protein (CRP), chest radiography, urine analysis and culture, 2 sets of central and peripheral automatized blood cultures, and cultures from other sites if clinically indicated.

Clinical Management and Follow-up

All children were managed by a study physician using the National Consensus on the Rational Approach towards Cancer Patients with FN.[30] This protocol includes guidelines for clinical and laboratory evaluations during hospitalization, empiric antibacterial and antifungal treatment, as well as antimicrobial adjustments. Antifungal selection was similar between hospitals and included amphothericin B as the first-line drug. Patients with a diagnosis of proven, probable, or possible aspergillosis were treated with voriconazole.[5]

All patients were evaluated clinically on a daily basis until they met criteria for episode termination defined as fever resolution and an ANC count ≥500/mm^3. ANC, AMC, and CRP were to be obtained daily in all episodes; for episodes with fever lasting for more than 3 days after admission, one or more of the following procedures were performed at day 4 on a patient-directed basis with the aim to determine absence or presence of an IFD: computed tomography scanner (computed tomography scan) for sinuses, chest, abdomen/pelvis, brain; heart ultrasound; bone scan; eye fundoscopy; GM antigen detection test; bronchoalveolar lavage; gastrointestinal endoscopy; and biopsies of lung and other tissues. If a bacterial or fungal culture from a sterile site resulted positive, repeat cultures were obtained every 48 to 72 hours until negativity; GM antigen detections were repeated at day 6, and from then on every 4 days until fever resolution.

Laboratory Procedures

Blood was incubated in BACT Alert 120 (Organon Teknika). All fungi (yeasts and molds) obtained from blood and other sterile sites, were identified to species level at the local laboratory, and then referred for confirmation to the Mycology Laboratory, Microbiology and Mycology Program of the Institute of Biomedical Sciences, Faculty of Medicine, Universidad de Chile. Antifungal susceptibility testing was performed for all yeast species isolated from blood.

GM was detected in serum by a direct double-sandwich ELISA (Platelia Aspergillus; Bio-Rad, Marnes-La-Coquette, France), according to manufacturer's instructions[31]; an index ≥0.5 was considered positive.

Definitions

Fever was defined as an axillary temperature ≥38.5°C in 1 measurement or ≥38°C in 2 consecutive measurements separated by 1 hour; severe neutropenia as an ANC ≤500/mm^3; profound neutropenia as an ANC ≤100/mm^3; monocytopenia as an AMC ≤100/mm^3. Aggressive and nonaggressive chemotherapy were defined based on the severity of medullar depression expected for the specific chemotherapy regimen. We considered aggressive all induction and consolidation chemotherapies used for acute lymphocytic/myeloid leukemia, relapse of leukemia, lymphomas, and induction chemotherapy for solid tumors or relapse of solid tumors. Maintenance therapies for any cancer type were defined as nonaggressive. Hypotension was defined as a blood pressure ≤fifth percentile adjusted to age and capillary refill delay as duration ≥3 seconds. Severe sepsis was defined as a systemic inflammatory response syndrome in the presence of, or as a result of, suspected or proven infection, plus one of the following: cardiovascular organ dysfunction, or acute respiratory distress syndrome, or 2 or more other organ dysfunctions.[32] IFD status were defined using the revised EORTC classification[29] as follows: proven if microbiologic or histologic evidence of fungal tissue invasion or positive fungal culture were obtained from a sterile body fluid, in addition to clinical or radiologic findings consistent with fungal infection. Probable IFD required 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 or cell-wall constituents). Possible IFD was defined as a case that met host factor and clinical criteria but lacked any mycologic documentation of infection; no IFD was defined as an episode that lacked presence of clinical and microbiologic evidence for IFD irrespective of the duration of fever.

Statistical Analysis

The following IFD groups were constructed for comparative analysis: all suspected IFD cases including proven, probable, and possible; proven and probable cases only; cases that did not have an IFD. Median and ranges were calculated for continues variables, which were compared using independent samples t tests if variances were homogenous according to the Bartlett Test for Inequality of Population Variances, and the data were approximately normally distributed. If variances were not homogenous or the data were not approximately normally distributed, the Mann-Whitney was used. Categorical variables were compared using the χ^2 with Yates correction and 2-tailed Fisher exact test when appropriate. Relative risks with the corresponding 99% CI were calculated for variables that were significantly different by univariate analysis. All statistical analyses were performed using the Epi Info Program, Version 3.5.1, 13/Aug/2008 (CDC, Atlanta, GA). We used a significance level of $P < 0.01$.

TABLE 1. Demographic, Clinical, and Laboratory Characteristics of the 17 Proven or Probable Invasive Fungal Disease Episodes

Age in Years/Gender	Cancer	Antifungal Onset Day*	Finding at the Time of Diagnosis of IFD				GM Day 4/6	Fungus Identified-Clinical Diagnosis
			T°	ANC	CRP	Images†		
Proven IFD								
16/Female	ALL relapse	2	39.4	286	97	None	1.16/0.20	*Candida albicans* in blood
2/Female	Solid tumor	3	39.0	66	142	None	0.83/ND	*C. albicans* in blood
14/Male	Solid tumor	6	39.0	1200	16	None	0.27/ND	*Candida tropicalis* in blood
2/Female	Solid tumor	4	36.9	0	233	Abd CT	ND/ND	*C. tropicalis* in blood-typhlitis
2/Male	ALL	7	38.8	0	123	Chest CT	0.16/0.13	*Aspergillus* in lung Bx-pneumonia
21/Female	ALL 2nd relapse	10	38.4	0	92	Chest/sinuses CT	ND/ND	Zygomicetes sinus Bx-pneumonia/ sinusitis
0.5/Male	ALL relapse	14	38.0	0	114	None	ND/ND	*Fusarium* in skin Bx and blood‡
Probable IFD								
2/Male	AML	7	38.1	0	446	Chest/sinuses CT	1.53/1.01	Pneumonia/sinusitis‡
6/Female	ALL	2	38	0	345	HUs	0.8/1.22	Endocarditis/esophagitis
6/Male	ALL	8	39.2	0	158	Chest CT/HUs	0.60/0.07	Pneumonia/endocarditis
6/Male	ALL	8	40.0	0	159	Sinuses CT	0.74/0.65	Sinusitis/prolonged fever§
7/Male	ALL	7	38.5	136	93	Chest/sinuses CT/HUs	0.54/1.34	Pneumonia/sinusitis/endocarditis
11/Male	AML	6	37.8	0	133	Chest/sinuses CT	0.56/0.64	Pneumonia/sinusitis
11/Male	ALL	4	39.6	0	170	Sinuses CT	0.54/0.55	Sinusitis
13/Male	ALL relapse	9	39.0	0	94	Chest CT	2.86/0.30	Pneumonia‡
14/Male	AML	6	38.5	0	219	Chest/Abd CT	5.9/1.7	Pneumonia/spleen nodules
15/Male	AML	8	39.0	0	221	Abd CT	0.63/0.62	Spleen/kidney nodules

*Date of antifungal onset after admission.

†Finding compatible with fungal infection in the indicated image; None means that imaging studies did not detect a finding suggesting a fungal infection in the child.

‡Child died during the FN episode, related with IFD.

§Prolonged fever not reasonably explained exclusively by probable fungal sinusitis.

IFD indicates invasive fungal disease; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; ANC, absolute neutrophil count; CRP, serum C-reactive protein; GM, galactomannan; ND, not done; CT, computed tomography; Abd, abdomen; HUs, heart ultrasound; Bx, biopsy.

RESULTS

Population Characteristics

A total of 936 FN episodes were admitted to the 6 participating hospitals during the study period. Of total, 646 episodes (69%) were classified as high risk for invasive bacterial infection, according to our predefined criteria, of which 604 were enrolled in the study. Reasons for exclusion were study team not contacted by treating physicians (N = 20), lack of compliance with inclusion criteria (N = 11), lack of complete clinical or laboratory evaluation at admission (N = 9), and consent refusal (N = 2). A total of 35 of 604 episodes (5.8%) had an IFD of which 7 (1.2%) were proven, 10 (1.6%) probable, and 18 (3.0%) possible IFD. No cases of IFD were diagnosed in low-risk FN episodes.

Description of IFD Episodes

Table 1 describes the relevant findings for the 17 cases of proven and probable IFD. The median age of children was 7 years (range, 0.5–13 years), 12 (71%) were male and most cases[14] occurred in children with a hematologic malignancy. The great majority of children with IFD had fever (16/17), profound neutropenia (14/17), and CRP values ≥90 mg/L (16/17) at the time of diagnosis. About 14 episodes were diagnosed after 3 days of fever. Of 7 proven IFD, 4 had fungemia (2 *Candida albicans*, and 2 *Candida tropicalis*), and 3 had mold infections with deep tissue involvement (1 *Aspergillus* sp, 1 *Fusarium* sp, and 1 Zygomycetes).

Characteristics of Febrile Neutropenic Episodes Within 24 Hours of Admission According to IFD Status

Age, gender, type of cancer, chemotherapy, hours of fever before admission to the hospital with a diagnosis of FN, use of an indwelling catheter, and AMC did not differ significantly between episodes that went on to develop or not develop an IFD (Table 2).

TABLE 2. Demographic, Clinical, and Laboratory Characteristics Obtained Within the First 24 Hours of Hospitalization by Invasive Fungal Disease Status

Characteristic	IFD Status		
	Proven/ Probable/ Possible (N = 35)	Proven/ Probable (N = 17)	No IFD (N = 569)
Age in years	8 (0.5–15)	7 (0.5–13)	7 (0.1–11)
Male gender	22 (63%)	12 (70%)	343 (60%)
Type of cancer			
Leukemia/lymphoma	23 (59%)	10 (59%)	324 (57%)
Leukemia/lymphoma relapse	7 (20%)	4 (24%)	93 (16%)
Solid tumors	5 (14%)	3 (18%)	115 (20%)
Aggressive chemotherapy	30 (86%)	14 (82%)	425 (75%)
Hours of fever prior to admission	5 (1–72)	12 (1–51)	3 (1–96)
Indwelling catheter in place	32 (91%)	14 (100%)	472 (83%)
Obtained at admission			
Presence of hypotension	11 (31%)	4 (23%)	98 (17%)
Capillary refill delay	9 (26%)*	5 (29%)	51 (9%)*
AMC ≤100	33 (94%)	16 (93%)	472 (83%)
Platelets ≤50,000	29 (82%)	12 (69%)	409 (72%)
CRP ≥90	21 (60%)	11 (65%)	221 (39%)
Obtained at 24 h			
Presence of hypotension	6 (17%)	5 (29%)†	51 (9%)†
Capillary refill delay	4 (11%)	4 (24%)‡	18 (3%)‡

Continuous variables are expressed as median (range) and only significant differences between groups are shown; categorical variables are expressed as the total number for each category and (percent).

*Relative risk (99% CI) 2.8 (1.2–6.4), $P < 0.01$.

†Relative risk (99% CI) 3.2 (1.1–9.1), $P < 0.01$.

‡Relative risk (99% CI) 7.4 (2.0–26.6), $P < 0.01$.

IFD indicates invasive fungal disease; AMC, absolute monocyte count; CRP, serum C-reactive protein.

TABLE 3. Clinical and Laboratory Characteristics Obtained at Day 4 of Hospitalization by Invasive Fungal Disease Status Diagnosed After 72 Hours of Admission

Characteristic	IFD Status Diagnosed After 72 h of Admission			Relative Risk Compared to No IFD	
	Proven/Probable/ Possible (N = 32)	Proven/ Probable (N = 14)	No IFD (N = 569)	Proven/Probable/ Possible	Proven/Probable
Presence of fever	32 (100%)	14 (100%)	227 (40%)	2.5 (2.1–2.8)	2.5 (2.1–2.9)
ANC ≤500	31 (97%)	13 (93%)	387 (68%)	1.4 (1.2–1.5)	NS
AMC ≤100	29 (93%)	14 (100%)	284 (50%)	1.8 (1.5–2.1)	2.0 (1.7–2.2)
CRP ≥90	22 (69%)	9 (64%)	193 (34%)	2.0 (1.4–2.8)	NS
Fever plus					
ANC*	31 (97%)	13 (93%)	187 (33%)	2.9 (2.4–3.5)	2.8 (2.2–3.6)
AMC*	29 (93%)	14 (100%)	153 (27%)	3.3 (2.6–4.2)	3.7 (3.1–4.4)
CRP*	22 (69%)	9 (64%)	125 (22%)	3.1 (2.1–4.5)	2.9 (1.6–5.0)
AMC and CRP	22 (70%)	10 (75%)	74 (13%)	5.2 (3.4–8.0)	5.4 (3.2–9.2)

NS = $P \geq 0.01$.
*Cut-off value used for ANC, AMC, and CRP are the same indicated above.
ANC indicates absolute neutrophil count; AMC, absolute monocyte count; CRP, serum C-reactive protein.

TABLE 4. Outcome of the Febrile Neutropenic Episode by Invasive Fungal Disease Status

Outcome	IFD Status			Significance Compared to No IFD	
	Proven/Probable/ Possible (N = 35)	Proven/ Probable (N = 17)	No IFD (N = 569)	Proven/Probable/ Possible	Proven/Probable
Days of					
Fever	12 (3–40)	11 (3–40)	3 (1–32)	<0.0001	<0.0001
ANC ≤500/mm^3	11 (2–40)	11 (2–29)	5 (1–34)	<0.0001	<0.0001
AMC ≤100/mm^3	10 (0–40)	9 (0–25)	3 (0–34)	<0.0001	0.001
Antibacterial treatment	19 (7–60)	20 (7–60)	10 (1–42)	<0.0001	<0.0001
No. episodes with					
Antifungal treatment	33 (94%)	16 (94%)	80 (14%)	6.7 (5.0–8.9)	6.6 (4.9–9.1)
Diagnosis of severe sepsis	24 (67%)	11 (65%)	127 (22%)	3.0 (2.1–4.3)	2.8 (1.7–4.7)
Admission to ICU	15 (43%)	7 (41%)	89 (16%)	2.7 (1.5–4.8)	2.6 (1.1–5.7)
Children that died	6 (17%)	4 (23%)	17 (3%)	5.7 (1.8–17.9)	7.8 (2.1–28.4)

Continuous variables are expressed as median (range) and categorical variables are expressed as the total n for each category and (percent); *P* values for continuous and relative risk (99% confidence interval) for significant ($P < 0.01$) variables are shown.
IFD indicates invasive fungal disease; ANC, absolute neutrophil count; AMC, absolute monocyte count; ICU, intensive care unit.

A significant higher proportion of episodes with hypotension and capillary refill delay within the first 24 hours of hospitalization were observed in IFD cases. A trend toward a higher proportion of cases with CRP ≥90 mg/L was observed for proven/probable/possible ($P = 0.02$) and proven/probable ($P = 0.06$) IFD compared with absence of IFD cases.

Day 4 Variables Associated With IFD Diagnosed After 72 Hours

Fever and neutropenia were present on day 4 in 218 of 604 (36%) FN episodes. Four variables differed significantly between IFD cases diagnosed after 72 hours of admission, when compared with cases not presenting an IFD: presence of fever, ANC ≤500/mm^3, AMC ≤100/mm^3, and CRP ≥90 mg/L (Table 3). The combination of 2 or more variables increased their performance as potential predictors for IFD. When comparing proven/probable IFD to no IFD, the combination of fever, AMC ≤100/mm^3, and CRP ≥90 mg/L at day 4 increased the RR to 5.4 (3.2–9.2). For this combination, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were 75 (95% CI, 43%–93%), 87% (83%–90%), 13% (6%–23%), and 99% (98%–99.8%), respectively. PPV increased to 26% (17%–37%), specificity remained unchanged, and sensitivity and NPV decreased to 70% (50%–81%) and 98% (96%–99%) when possible IFD cases were added to the analysis. For the 461 episodes occurring in children with hematologic malignancies, the analysis provided similar RR, PPV, and NPV for individuals and combined variables.

Outcome of the Febrile Neutropenic Episode by IFD Status

Episodes with an IFD had a more severe outcome (Table 4). Duration of fever, ANC ≤500/mm^3, AMC ≤100/mm^3, and antimicrobial use were significantly more prolonged when compared with episodes not developing an IFD. Diagnosis of severe sepsis and the need for admission to an intensive care unit were more common in IFD cases. The great majority of episodes catalogued as having an IFD received antifungal treatment (94%) including episodes classified as possible. The 2 children not receiving antifungal were discharged in good clinical condition after 16 and 13 days of antibacterial therapy with fever lasting 8 and 10 days and neutropenia lasting 17 and 10 days, respectively.

Antifungals were used by treating physicians in 80 of 569 (14%) episodes that were classified after discharge as not having developed an IFD by the study evaluators, of which 64 (80%) had fever >72 hours. Conversely, treating physicians did not prescribe an antifungal in 154 episodes despite of fever lasting >72 hours (range: 4–24 days).

More children with an IFD died during the FN episode with a RR ranging from 5.7 to 7.9 depending on inclusion of possible IFD cases. Of the 6 children dying with a proven/probable/possible IFD, 4 could be attributed to the IFD: 1 proven, 2 probable, and 1 possible. The first 3 are mentioned in Table 1.

DISCUSSION

In this prospective, multicenter study, the overall incidence of IFD was 5.8% among 604 HRFN episodes, half of which were proven or probable according to EORTC/Mycoses Study Group criteria. The overall incidence is lower than our previous study,[26] probably related with the use of more strict criteria and improved diagnostic tools for exclusion of non-IFD cases.[29]

IFD occurred among children admitted with HRFN and the majority of IFD episodes were diagnosed after day 3 of hospitalization. Children presenting hypotension and/or capillary refill delay within 24 hours of admission were at higher risk for developing an IFD. More importantly, we identified 4 variables that at day 4 of hospitalization were significantly different for IFD and non-IFD episodes. Of these, the combination of fever, AMC $\leq 100/mm^3$, and PCR ≥ 90 mg/L was greater than 5 times the risk of developing an IFD compared with episodes lacking one or more of these variables. The above combination had a relatively high sensitivity (75%), specificity (87%), and NPV (99%) but a relatively low PPV (13%) if only proven/probable episodes were included, increasing to 26% when possible episodes were included.

To our knowledge, these are the first results obtained from a prospective pediatric population that identify a useful combination of clinical and laboratory variables that at day 4 reasonably discriminate episodes that will develop IFD from those that will not. Several research groups are searching for early biomarkers of IFD infection with the aim to rapidly identify and treat episodes with a high IFD probability and avoid treatment based only on prolonged fever and neutropenia.[33–35] Portugal et al evaluated the combination of intensity and duration of neutropenia, concluding that this measure can be a good predictor for invasive mold infections in adult populations with acute myeloid leukemia[36]; prospective studies are needed to validate their finding. Our study adds monocytopenia and increased serum CRP to the short list of biomarkers significantly associated with IFD.

Empiric antifungal therapy has become standard of care and is usually administered to patients with persistent fever and neutropenia despite appropriate antibacterial coverage.[20] However, this approach is not patient directed, resulting in a significant number of unnecessary antifungal treatments. Our findings provide new potential markers of risk for IFD that can aid in moving from empiric to pre-emptive antifungal therapy in this population.

One limitation of our study is that half (18/35) of the IFD episodes were classified as possible, despite our efforts to identify a fungus. This issue highlights the need for continued efforts to improve the etiologic diagnosis of IFD. Promising methods include indirect mycologic diagnostic test, such as the detection of GM in body fluids other than serum and plasma, of ß-D-glucan in serum, and of fungal deoxyribonucleic acid in body fluids by PCR.[37–40]

To our knowledge, this is the first large pediatric cohort study that provides a combination of biomarkers that reasonably discriminates children with cancer and FN with prolonged fever that are at a higher risk for IFD. A prospective validation is required before we can propose to use this combination for the adoption of a more selective management strategy for IFD based on pre-emptive treatment of children at high-risk for IFD.

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