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Factors Associated to Invasive Fungal Infection in Hispanic Patients with Hematological Malignancies

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Abstract

Fungal infections represent a serious complication for immunosuppressed patients resulting in an increased morbidity and mortality.

A non-concurrent prospective study was performed to evaluate the factors associated to invasive fungal infection (IFI) in patients with hematological malignancies admitted to the University Hospital in San Juan, Puerto Rico from January 1st, 2011 through June 15th, 2014.

The medical records of 84 patients were evaluated. Fifty-nine patients with IFI and twenty-five without IFI. The majority were men between 35 to 55 years old. The main hematological diagnosis was acute myelogenous leukemia (AML) followed by acute lymphoblastic leukemia (ALL). Seventy-percent developed IFI. The most common fungi were *C. albicans* followed by non-albicans species, Fusarium and, Aspergillus species, respectively. About 63% of the patients with AML and 81% without AML had IFI. Those who received steroids were more likely to develop IFI. After adjusting for AML and age, the odds of IFI among patients using steroids were 3.33 higher than those not using steroids. Patients who were exposed to different antifungal medication had 72% lower odds to develop IFI.

Keywords

Invasive fungal infection; Hematological malignancies; Hispanic

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Conflicts of interests

The authors have no conflict of interest to disclose.

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Background

Fungal infections represent a serious complication for immunosuppressed patients. Fusarium and Aspergillus species have been recently recognized as emerging pathogens, particularly in patients with hematologic malignancies resulting in an increased morbidity and mortality (1–5). Aspergillus has remained the leading cause of increased morbidity and mortality but Fusarium species have increased in frequency to the point that now represents the second most frequent cause of invasive fungal infections (IFI) (2). Incidence rates of 13%–21% have been reported with an overall mortality as high as 50% of cases (6–8). Failure to establish a prompt diagnosis may result in a delay in the initiation of adequate antimicrobial therapy, interrupting malignancy treatment and worsening the prognosis.

IFI was an independent risk factor for mortality and increased length of hospital stay in patients with cancer and febrile neutropenia in a recent study (6). Moreover, the United States National Center of Health Statistics showed an overall increase in mortality from mycotic infections between 1980 and 1997, more evident for aspergillosis (357% increase) and for other mycoses (329% increase) (9). Given increase in morbidity and mortality associated with these types of infections, patient with neutropenia are often started on empiric antifungal therapy in an attempt to improve survival (10–11).

In our center most patients receive autologous bone marrow transplant and chemotherapy for acute myelogenous leukemia (AML). These patients are at an even higher risk to develop IFI (12). It is essential to assess the general risks and vulnerability of our population in order to improve outcomes. Risk factors have not been studied in our population. Therefore, we aimed to assess patients with hematological malignancies that have been diagnosed and/or treated for IFI in the Leukemia/Lymphoma and the Hematopoietic Stem Cell Transplant Unit of the University Hospital in San Juan Puerto Rico.

Patients and methods

All patients with IFI while cared for at the Leukemia, Lymphoma and Hematopoietic Stem Cell Transplant Unit of the University Hospital in San Juan, Puerto Rico, from January 1st, 2011 through June 15th, 2014 were identified by a review of the clinical records. A standardized data sheet containing the pertinent clinical information were completed by all investigators and sent for analysis. The diagnosis of IFI was classified as proven, probable, or possible, according to previously established criteria by the European Organization for Research and Treatment Cancer/Invasive and Mycosis Study Group (13). Briefly, proven IFI was defined as the growth of fungi species in cultures of blood or samples obtained from other sterile sites in patients with clinical signs of infection or the demonstration of hyphae in tissue together with recovery of fungal species from the same tissue. Probable IFI was defined as the growth of fungi species from respiratory tract secretions obtained from patients with clinical signs of infection compatible with fungi in the absence of other pathogens. Patients with positive cultures of skin lesions (e.g., cellulitis, nodules) without histopathologic demonstration of hyphae were also included in this category. Cases of possible infection were excluded.

Survival was defined as the time between the date of diagnosis of IFI and death or last follow-up. The date of diagnosis was defined as the day of the first culture positive for IFI or date of biopsy. If the diagnosis of IFI was made postmortem, the date of death was considered the date of diagnosis.

Persistent neutropenia was defined as an absolute neutrophil count (ANC) of less than 500 neutrophils/mm3 or ANC that is expected to decrease to less than 500 neutrophils/mm3 during the next 48 hrs (14). Disseminated infection was defined as involvement of more than 2 noncontiguous organs. The following variables were analyzed: age, sex, comorbidities, type and, status of underlying disease, sepsis, concomitant bacterial infection, previous antibiotic use, presence of neutropenia, use of corticosteroids, extent of fungal infection (localized or disseminated), antifungal therapy, type of chemotherapy used, length and, type of antibiotic use, and, physical localization within the Unit. International Review Board approval # A0690114.

Statistical Analysis

Descriptive statistics and graphs were used to characterize overall sample and according to their IFI status. Fisher's Exact test, Chi-squared test or Student's T test were performed, when appropriate, to determine association between IFI and characteristics of hematological malignancies patients. Also, a logistic regression was performed to estimate unadjusted and adjusted odds ratios (OR) using 95% confidence intervals (95% CI). Interaction terms between potential confounder variables and main predictors were assessed using the Likelihood Ratio test. All statistical analyses were performed by the research design and biostatistics core of the Puerto Rico Clinical and Translational Research Consortium using the statistical package STATA v.14 (Stata Corp. Texas, USA).

Results

The medical records of 84 patients admitted during the study period were evaluated, 59 with IFI and 25 without IFI. The majority of the patients were men (58%) and was between 35–55 years of age (37%). The main hematological diagnosis was AML (60·7%) and acute lymphoid leukemia (21·4%). Two patients had more than one hematological diagnosis: 1) AML and Hodgkin lymphoma, and, 2) Acute lymphoid leukemia and Non-Hodgkin lymphoma. Patients' characteristics were also assessed according to IFI status (Table 1). Seventy percent of patients with hematological malignancies had an IFI (Table 1). The most common fungi were C. *albicans* (35·6%) followed by C. tropicalis (23·7%) and, C. parapsilosis (18·6%) (Table 1 and Figure 1). About 84·3% of patients with IFI had a concomitant bacterial infection; Gram (+) cocci (not MRSA) were the most common bacteria followed by MDR Gram (−) bacilli (Table 1).

Similar proportions of men and women had IFI (71% and 69%, respectively; Table 1). About 63% of the patients with AML and 81% of patients without AML had IFI (p=0·07). Patients who received steroids were more likely to have IFI than patients that did not receive steroids (84·2% vs. 15·8%, p=0·02). After adjusting for AML and age, the odds of IFI among patients using steroids were 3·26 (95%CI: 1·03–10·33) higher than those not using steroids

(Table 2). The exposure to antifungal medication was significantly associated to IFI (63·6% using different classes of antifungals vs. 86·1% using single antifungal; not combined; p=0·03). Patients using different classes of anti-fungal medications had 72% lower odds of IFI (95%CI: 0·09–0·95) than patients using single anti-fungal medication. Neither age, comorbidities, principal diagnosis, presence of intravascular catheters, parenteral nutrition, nor, concomitant bacterial infection showed a statistically significant association with IFI (p>0·05; Table 1). Location of patients at the Leukemia Unit was not related to IFI (p>0·05, Figure 2).

Discussion

To the best of our knowledge, this is the first study performed in Puerto Rico evaluating the risks factors of IFI in hematological patients. The significant variables associated to fungal infection identified were the use of steroids and exposure to antifungals while on chemotherapy hematological, both more commonly seen in patients with AML.

Other studies have shown a similar risk with the use of steroids in similar populations (15–17). Steroids add a significant risk to develop IFI in the setting of immunosuppression and by consequence strongly associated to sepsis and mortality (18). Other studies have identified common risk factors to develop IFI but samples are not comparable with this study (19–21).

Neutropenic fever usually requires an initial empiric antimicrobial therapy before a definite diagnosis is evident. Available guidelines have specific parameters for when to start empiric therapy and with what agents (14). Those who are exposed to several agents are generally much more critically ill. Unexpectedly, we found that exposure to different antifungal classes provide a protective effect to IFI.

The incidence of non-albicans species has recently increased in patients with hematological malignancies as shown in our findings (non-albicans n=25 vs albicans n=21) (22–23). Candida *albicans* was noted to be the most common cause of IF in our study. This type of infection is associated with the highest fatality rate in immunocompromised patients and third leading overall cause of infection globally (24–29). The incidence of Candida-related blood stream infection in our medical center had been previously studied by Conde et.al in 2010 and found that Candida parapsilosis was the most common Candida spp. identified (30). The sample in that study was much broader including general medical wards and intensive care units, likely explaining discordance with our findings.

Given previous clinical experience by Infectious Diseases service in our hospital, Aspergillus and Fusarium were expected to be the most common causes of IFI in our setting. However our data showed that Candida spp. is the most common. We theorize that since their diagnosis is difficult given insidious onset, they might be underrepresented in our sample.

Conclusion

Our data showed an increased risk of IFI in patients with AML and those receiving steroids. Those who were exposed to different classes of antifungals significantly reduced the risk to develop IFI.

Among identified fungal organisms, Candida *albicans* was the most common fungal organisms identified followed by non-albicans, Fusarium and, Aspergillus species, in that order. Contrary to what has been reported in literature, Fusarium is more prevalent than Aspergillus in our hematological population. Therefore, high degree of suspicion is needed in order to provide adequate empirical antifungal coverage for patients at high risk before a definite diagnosis can be made.

Limitations

This was a retrospective and single-center study taking into account only a small sample of participants; therefore other studies that have tried to identify risks factors for IFI are not comparable if we take into consideration the sample size.

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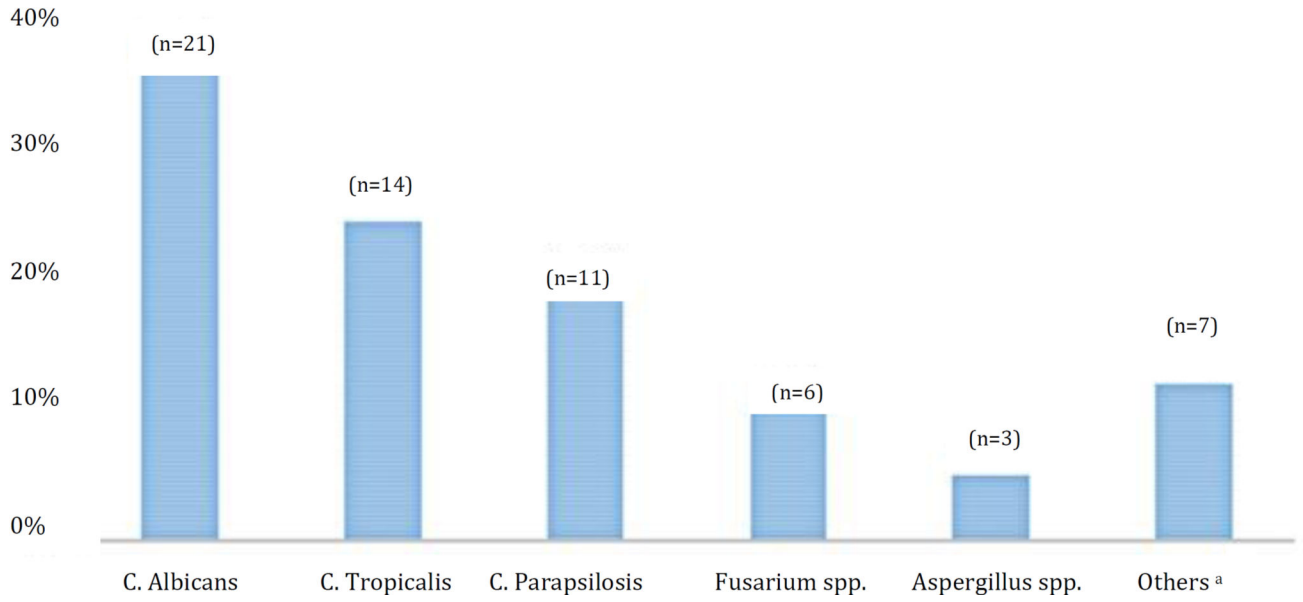

FIGURE 1.

Distribution of invasive fungal organism among hematological patients with fungal infection (n=59).

Note: Patients with concomitant fungi infections were counted at each one of their infections; the following concomitant infections were observed: 1) C. Albicans + Aspergillus spp., 2) C. Tropicalis + C. Albicans, and 3) Aspergillus spp. + Fusarium spp.

[a]Includes: Rhizopus, C. Krusei, C. Lusitaniae, Acremonium, Trichophyton Rubrum, and, Trichosporum Asahii.

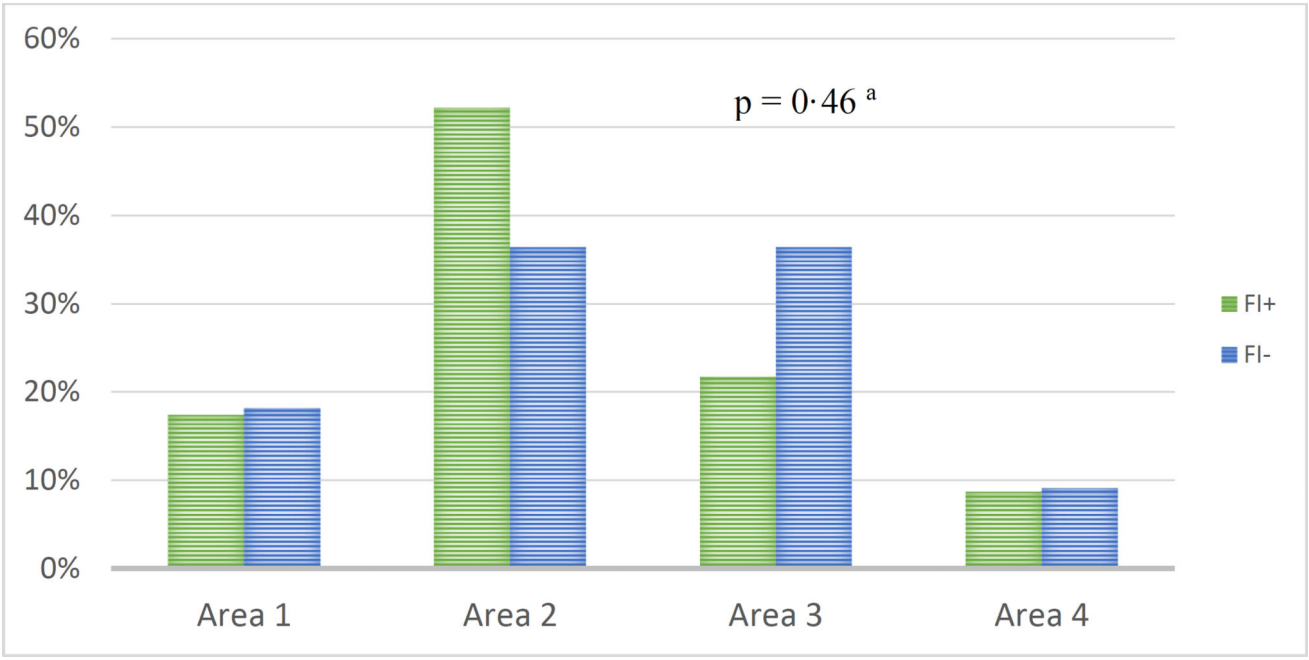

FIGURE 2.

Location of patients at the Leukemia/Lymphoma Unit by fungal infection status (n = 84). Abbreviations: FI+, patients with fungal infection; FI−, patients without fungal infection. Note: Area 1, rooms 401–403; Area 2, rooms 404–408; Area 3, rooms 409–411; Area 4, Transplant unit.

[a]Fisher's Exact test was performed.

TABLE 1

Characteristics of patients with haematological malignancies according to fungal infection status (n=84).

Characteristics[a]	Fungal Infection YES n = 59 n (%)	Fungal Infection NO n =25 n (%)	P–value[b]
Sex			0·78[c]
Woman	24 (68·6)	11 (31·4)	
Men	35 (71·4)	14 (28·6)	
Age (in years)			0·38
21–34	12 (80·0)	3 (20·0)	
35–54	19 (61·3)	12 (38·7)	
55–70	19 (67·9)	9 (32·1)	
>70	8 (88·9)	1 (11·1)	
Living environment			0·32[c]
Urban	26 (65·0)	14 (35·0)	
Rural	33 (75·0)	11 (25·0)	
Comorbid conditions			
Diabetes Mellitus	18 (66·7)	9 (33·3)	0·70[c]
Hypertension/CAD	31 (72·1)	12 (27·9)	0·60[c]
Bronchial Asthma	3 (75·0)	1 (25·0)	>0·99
Thyroid Dysfunction	7(100·0)	0 (0·0)	0·10
HIV	2 (66·7)	1 (33·3)	>0·99
Chronic kidney Disease[d]	6 (85·7)	1 (14·3)	0·43
Chronic Liver Disease	2 (66·7)	1 (33·3)	>0·99
Survival			0·61[c]
Dead	22 (73·3)	8 (26·7)	
Alive	36 (63·9)	17 (32·1)	
Hematologic Malignancy			0·99[c]
Newly Diagnosed	39 (69.6)	17 (30.4)	
Reoccurrence	16 (69.6)	7 (30.4)	
Principal Dx			
Acute Myeloid Leukemia	32 (62·7)	19 (37·3)	0·07[c]
Chronic Myeloid Leukemia	4 (100·0)	0 (0·0)	0·23[e]
Acute Lymphoid Leukemia	14 (77·8)	4 (22·2)	0·56[c]
Non-Hodgkin Lymphoma	4 (80·0)	1 (20·0)	0·52[e]
Hodgkin Lymphoma	1 (50·0)	1 (50·0)	0·51[e]
Bone Marrow results at day 14			>0·99
Mean ± SD	2·5 ± 1·1	2·5 ± 1·1	

Characteristics[a]	Fungal Infection YES n = 59 n (%)	NO n =25 n (%)	P–value[b]
Bone Marrow Iron Stores			>0·99
Decreased/Few bits	2 (50·0)	2 (50·0)	
Adequate	3 (42·9)	4 (57·1)	
Increased/Markedly Increased	5 (50·0)	5 (50·0)	
Acute Renal Failure	25 (64·1)	14 (35·9)	0·25[c]
Sepsis during hospitalization	43 (68·25)	20 (31·75)	>0·99
Broad Spectrum Antibiotics	57 (70·4)	24 (29·6)	0·31[e]
Renal Replacement Therapy	5 (62·5)	3 (37·5)	0·70
Total Parenteral Nutrition	10 (83·3)	2 (16·7)	0·20
Use of steroids before dx	**32 (84·2)**	**6 (15·8)**	**0·02**[c]
Surgery	13 (86·7)	2 (13·3)	0·12
Days on ventilation			0·86
0 days	29 (65·9)	15 (34·1)	
1 – 10 days	9 (75·0)	3 (25·0)	
>10 days	7 (63·6)	4 (36·4)	
Antifungal Medications			0·07
Azoles	16 (88·9)	2 (11·1)	
Echinocandins	8 (100·0)	0 (0·0)	
Amphotericin B	7 (70·0)	3 (30·0)	
Combination or different classes	21 (63·6)	12 (36·4)	
Intravenous Access			0·11[e]
Central	39 (73·6)	14 (26·4)	
Peripheral	6 (50·0)	6 (50·0)	
Bacterial Organism			
Gram positive cocci (not MRSA)	23 (74·2)	8 (25·8)	0·59[c]
MRSA	3 (100·0)	0 (0·0)	0·56
Gram negative bacilli (not MDR)	9 (69·2)	4 (30·8)	>0·99
Gram negative bacilli MDR	12 (60·0)	8 (40·0)	0·21[c]
S. maltophilia	3 (50·0)	3 (50·0)	0·35
Bacterial Site			
Lung	7 (70·0)	3 (30·0)	>0·99
Bloodborne	28 (75·7)	9 (24·3)	0·36[c]
Skin/Soft Tissue	7 (63·6)	4 (36·4)	0·72
Urinary Tract	11 (68·7)	5 (31·3)	>0·99[c]

Abbreviations: MRSA, Methicillin resistant staphylococcus aureus; MDR, Multi drug resistant.

[a]Total may not equal the overall sample size except for the following characteristics: sex, living environment, comorbid conditions, and acute renal failure;

[b] Two-sided Fisher's Exact test or Student's T test was performed, as appropriate, unless otherwise specified;

[c] Chi-square test was performed;

[d] With or without haemodialysis;

[e] One-sided Fisher's Exact test was performed.

TABLE 2

Logistic regression analysis of risk factors for fungal infection.

	Crude OR (95%CI)	Adjusted[a] OR (95%CI)
AML		
No	1·0	1·0
Yes	0·39 (0·14–1·11)	0·48 (0·14–1·70)
Use of Steroids		
No	1.0	1·0
Yes	3·65 (1·19–11·20)	3·26 (1.03–10·33)
Combination (different classes) of antifungal medications		
No	1·0	-
Yes	0·28 (0·07–0·92)	

Abbreviations: OR, Odds Ratios; AML, Acute Myeloid Leukemia

[a]AML, use of steroids and, age were included in the model.