Antifungal Prophylaxis and Risk for Invasive Mold Infections in Children with Hematologic Malignancies

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Introduction:

Invasive mold infections (IMI) are a leading cause of mortality in immunocompromised hosts. Children diagnosed with hematologic malignancies experience profound, prolonged neutropenia following intensive chemotherapy, and are at increased risk for infection-related outcomes. Depending on the anticipated therapeutic intensity, antimicrobial prophylaxis may be employed to mitigate risk for infection. We conducted a retrospective review of children diagnosed with acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), or lymphoma between 2006-2015 and determined the incidence of IMI to be 4.8% (47/976), with an exceptionally high incidence observed in patients with AML (8.1%). This observation prompted a change in clinical practice that broadened prophylaxis for high risk patients to include coverage of molds, and resulted in development of a risk-stratified algorithm for antifungal prophylaxis in children with hematologic malignancies. The objective of this study was to evaluate the change in IMI incidence post-implementation of this algorithm, and to identify host factors contributing to risk for IMI in children with hematologic malignancies.

Objective:

The objective was to compare the incidence of IMI pre/post implementation of antifungal prophylaxis decision tree. Also, it was planned to evaluate the impact of race/ethnicity on the development of IMI in children with hematologic malignancies.

Methods:

We conducted a retrospective review of children ≤ 21 years old and diagnosed with ALL, AML, or lymphoma between 2016-2019, and were treated for IMI between 2016 and June 2020. To identify potential cases, we employed a strategy identical to the one used in the 2006-2015 review, specifically, a search of the electronic medical record utilizing ICD9 codes broadly inclusive of relevant cancer and fungal diagnoses. Each potentially eligible case was then reviewed for the following inclusion/exclusion criteria (also identical to the prior review): diagnosis and treatment of ALL, AML, or lymphoma

at Texas Children's Hospital, diagnosis of IMI that met criteria for 'proven' or 'probable' per the European Organization for Research and Treatment of Cancer/Mycoses Study Group and occurring prior to stem cell transplant, and no underlying immunodeficiency or history of solid organ transplant. Host and disease-related factors, as well as IMI incidence, were compared for 2006-2015 vs. 2016-2020 using a Chi-square, Fisher, or Student t-test as appropriate, and host factors predictive of IMI were assessed by multivariable linear regression.

Results:
The overall incidence of proven/probable IMI in children diagnosed with hematological malignancies between 2006-2019 was 4.2% (61/1456). The incidence of IMI decreased from 4.8% to 2.9% between 2006-2015 and 2016-2020. For specific diagnoses, the rate of IMI decreased from 5.0% to 3.6% (ALL, 35/705 vs. 10/276), from 1.9% to 1.4% (lymphoma, 47/976 vs. 14/480), and from 8.1% to 3.2% (AML, 9/111 vs. 2/62). No significant differences in host factor or disease-related characteristics were noted when comparing IMI cases in 2006-2015 vs. 2016-2020, nor were there differences in the proportion of patients in relapse at the time of IMI or taking antifungal prophylaxis. Substantial differences in representative mold species were noted between the two-time periods, e.g. Aspergillus spp. accounted for 19/47 IMI from 2006-2015, but accounted for none of the IMIs diagnosed 2016-2020. In 2016-2020, 5/14 IMI were due to Trichosporon spp., with 4/14 Rhizopus spp., 2/14 Fusarium spp., 1/14 Curvularia spp., 1/14 Histoplasma spp., and 1 that met criteria for probable IMI. In multivariable analyses (Table 1), Hispanics were more likely to develop an IMI than non-Hispanics (p=0.04, OR 1.94, CI 1.03-3.66), and those with lymphoma were less likely to develop an IMI than those with ALL (p=0.03, OR 0.33, CI 0.12-0.87). Patients diagnosed between 2016-2019 were substantially less likely to develop IMI than those diagnosed 2006-2015 (p=0.003, OR 0.33, CI 0.16-0.69).

Discussion and Conclusion:
In this single institution study, risk for IMI in children with hematologic malignancies declined significantly after implementation of an antifungal prophylaxis algorithm that broadened coverage for high risk populations. Hispanics were at higher risk for IMI than non-Hispanics, suggesting a need to investigate relevant factors contributing to this disparity. This project can be used to further investigate the factors that contributed to invasive mold infections using a larger study populations. We can then continue to explore the potential contributing factors to the racial and ethnic disparities by including potential contributing factors such as socioeconomic factors and genetic risk.

Table 1: Multivariable analysis of Proven/Probable IMI (n=61) vs. No Proven/Probable IMI (n=1,395) in Children Diagnosed with Hematologic Malignancies between 2006 and 2019

	Univariable		Multivariable	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Sex				
Male	ref		ref	
Female	1.14 (0.68-1.91)	0.62	1.21 (0.71-2.05)	0.48
Age at diagnosis				
≤ 1 year	ref		ref	
>1, <10 years	0.48 (0.20-1.14)	0.10	0.50 (0.20-1.25)	0.14
≥10 years	1.02 (0.44-2.37)	0.96	1.45 (0.60-3.47)	0.41
Race				
White	ref		ref	
Black	0.59 (0.21-1.66)	0.32	0.89 (0.29-2.79)	0.85
Asian	1.35 (0.53-3.48)	0.53	2.12 (0.73-6.12)	0.17
Other/Multi	--	--	--	--
Ethnicity				
Non-Hispanic	ref		ref	
Hispanic	1.72 (1.01-2.94)	0.05	1.94 (1.03-3.66)	0.04
Year of cancer diagnosis				
2006-2015	ref		ref	
2016-2019	0.34 (0.17-0.70)	0.003	0.33 (0.16-0.69)	0.003
Cancer diagnosis				
ALL	ref		ref	
AML	1.41 (0.72-2.79)	0.32	1.29 (0.62-2.67)	0.49
Lymphoma	0.35 (0.14-0.89)	0.03	0.33 (0.12-0.87)	0.03

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