Risk Factors for Invasive Fungal Disease in Pediatric Cancer and Hematopoietic Stem Cell Transplantation: A Systematic Review

Running Title: Fungal Infection Risk Factors in Pediatric Cancer

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ABSTRACT

**Background**: While a number of risk factors have been associated with invasive fungal disease (IFD), a systematic review of the literarture documenting pediatric specific factors has not been performed.

**Methods**: We used the Ovid SP platform to search MEDLINE, MEDLINE In-Process and Embase for studies that identified risk factors for IFD in children with cancer or HSCT recipients. We included studies if they consisted of children or adolescents (< 25 years) who were receiving treatment for cancer or undergoing HSCT and if the study evaluated risk factors among patients with and without IFD.

**Results**: Among the 3,566 studies screened, 22 studies were included. A number of pediatric factors commonly associated with an increased risk for IFD were confirmed, including prolonged neutropenia, high dose steroid exposure, intensive timing chemotherapy for acute myeloid leukemia, and acute and chronic graft versus host disease. Increasing age, a factor not commonly associated with IFD risk, was identified as a risk factor across multiple published cohorts.

**Conclusions**: This systematic review confirms risk factors for IFD that are routinely considered in daily clinical practice. Increasing age should also be considered when assessing risk for IFD. Future efforts should focus on defining more precise thresholds for a particular risk factor (i.e. age, neutropenia duration) and on development of prediction rules inclusive of individual factors to further refine risk prediction.

BACKGROUND

 Children with cancer or those who undergo hematopoietic stem cell transplantation (HSCT)[1-3] are at risk for invasive fungal disease (IFD) and IFDs are an important contributor to morbidity and mortality. Systematic identification of risk factors for IFD is a necessary step to stratify patients into high and low risk groups. This risk stratification can then serve as the foundation for development of efficient supportive care guidelines that will inform clinical decisions relevant to the management of IFD, such as when to perform fungal diagnostic testing and when to initiate empiric antifungal therapy.

 Several narrative reviews have described risk factors for IFD.[4,5] A systematic review is a more methodologically rigorous approach as it ensures that all eligible studies are included, their methods are assessed, and the published data are comprehensively used to inform IFD risk designation. Such efforts are now ubiquitous throughout medicine, including the development of risk prediction rule for microbiologically documented infection in pediatric fever and neutropenia.[6] However, no such comprehensive effort has been conducted to identify factors associated with IFD in pediatric cancer and HSCT recipients.

 The objective of this systematic review was to identify risk factors for IFD in pediatric cancer or HSCT patients. These risk factors can then be used to inform high and low risk stratification for IFD in this patient population.

METHODS

 This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations for reporting.[7]

Briefly, PRIMSA is a methodology developed to assist researchers in performing systematic reviews and meta-analyses. Among other things, PRISMA provides guidance to authors on developing an *a priori* plan for the systematic review and includes a checklist of items to be included in the study protocol. The overarching goal of PRISMA is to improve the conduct and quality of published systematic reviews through standardization of practice.

Data Sources and Searches

 We used the Ovid SP platform to search MEDLINE, MEDLINE In-Process and Embase for articles indexed up to March 14, 2016. The search strategy included the Medical Subject Heading terms and text words aimed to identify publications describing factors associated with IFD among children and adolescents (< 25 years) with cancer or undergoing HSCT. The full search strategy is shown as Appendix 1. The set was limited to studies published in 1980 or more recently. There was no restriction by language.

Study Selection

 Eligibility criteria were established *a priori*. Studies were included if subjects were (1) children or adolescents with cancer or were HSCT recipients,(2) publication was a fully published primary study, and (3) study described the number of patients with IFD and factors associated with IFD. Reasons for excluding studies were as follows: (1) Not a full text publication, (2) Included patients aged 25 years and older, (3) Less than 90% of patients had cancer or were HSCT recipients, (4) Did not describe the number of patients with IFD, (5) Did not have a control group or did not compare the risk of IFD between patients with and without a risk factor of interest, (6) Less than 10 patients with IFD evaluated, (7) *Pneumocystis jirovecii* was the only fungal pathogen examined, and (8) Only assessed effectiveness of prophylactic anti-fungal therapy.

 Two reviewers (PR and LS) independently evaluated the titles and abstracts of publications identified by the search strategy and all potentially relevant publications were retrieved in full. These same two reviewers evaluated full text articles to decide whether eligibility criteria were met. Final inclusion of studies into the systematic review was by agreement of both reviewers. We described agreement regarding study inclusion using the kappa statistic; agreement was defined as slight (0 to 20%), fair (21 to 40%), moderate (41 to 60%), substantial (61 to 80%) or almost perfect (81 to 100%).[8]

Data Abstraction and Methodological Approach

 Two reviewers (PR or LS) abstracted all data from the publications in duplicate and any discrepancies were resolved by consensus. The primary variables of interest were risk factors for IFD including underlying diagnosis, treatment including steroids, neutropenia, and other factors. Results of multiple regression or other adjusted analyses were displayed preferentially. Studies were stratified by those which evaluated for IFD risk throughout the duration of a chemotherapy treatment period or following HSCT versus those who evaluated IFD risk specifically during periods of fever and neutropenia.

 Study attributes abstracted included years of study publication and enrollment, patient age range, patient population (cancer, HSCT or both) and specific population details, and study design. We also recorded the setting in which IFD risk was evaluated (for example, during treatment, post-HSCT or during fever and neutropenia), antifungal prophylaxis, whether IFD was defined using the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) consensus criteria, the definition of cases and how possible IFDs were handled. Finally, we abstracted statistically significant risk factors. If both univariate and multiple regression were conducted, only multiple regression (if sufficient number of events were evaluated) was shown. Meta-analysis was not planned because excessive heterogeneity was expected, and a narrative approach to synthesizing the data was undertaken.

Assessment of Study Quality

 Two reviewers (PR and LS) assessed study quality and any discrepancies were resolved by consensus. Study quality was evaluated using a modified version of an instrument previously developed to describe quality in studies of prognosis.[9] This quality assessment instrument examines four potential sources of bias: study participation, study attrition, confounding variables and measurement of outcomes. Relevant to this systematic review, we abstracted data on bias related to study participation, confounding variables and measurement of outcomes; they were rated as having low, high, or uncertain risk of bias.[9]

RESULTS

Figure 1 illustrates the flow of study publication identification and selection. There were 3,566 unique citations identified by the search strategy, of which 51 were retrieved for full-text evaluation. Among these publications, 22 met the eligibility criteria and were included in the systematic review (Table 1). Reasons for exclusion are described in Figure 1. Agreement in study inclusion between the two reviewers was perfect with kappa=100%.

 In terms of patient population enrolled, 8 studies[10-17] enrolled only HSCT patients of which six enrolled only allogeneic HSCT patients. There were 10 studies that exclusively enrolled cancer patients[1,18-26], although some of these patients may have undergone HSCT after enrollment. Both cancer and HSCT recipients were included in four studies.[27-30] Among the 22 publications, 18 (82%) assessed IFD risk throughout the duration of the chemotherapy treatment period or post HSCT period[1,10-23,27-29] with the remaining four (18%) assessing IFD risk only in the time frame of fever and neutropenia.[24-26,30] Fourteen (64%) studies used the EORTC/MSG criteria to classify IFD.[31]

 Across the identified studies a variety of potential risk factors for IFD were evaluated, including underlying diagnosis, age, graft versus host disease (GVHD), neutropenia, and immunosuppressive agents such as chemotherapy, corticosteroids and HSCT conditioning regimens (Supplemental Table). Various diagnoses were statistically significantly associated with IFD (Table 2). Acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL)[22,29]portended an increased risk for IFD relative to other cancer diagnoses, while AML was associated with a greater risk for IFD than ALL.[21,26] Among HSCT recipients, both severe aplastic anemia and Fanconi anemia as the indication for transplant were associated with increased risk for IFD.[15]

 Neutropenia, defined in various ways (e.g. absolute neutrophil count (ANC) below 100 cells/μL or duration of neutropenia more than 28 days), was found to be associated with IFD in 6 different studies; three of these studies were in children with leukemia, two were HSCT cohorts, and one included both HSCT recipients and cancer patients. Among leukemia patients, neutropenia at the start of chemotherapy[1] or a decline in the ANC below 100 cells/μL[23] were each associated with increased risk of IFD. In HSCT cohorts, duration of neutropenia in days[17], as a continuous variable was found to increase the risk for IFD and neutropenia duration dichotomized at a threshold of more than 28 days[15] was significantly associated with IFD.

 Certain corticosteroid exposures, chemotherapy courses and conditioning regimens were associated with increased IFD. Exposure to high dose corticosteroids was correlated with an increased risk for IFD in three separate HSCT cohorts,[11,15,17] while the duration of steroid exposure was associated with IFD in one cohort of AML patients1 and a second study inclusive of HSCT and cancer patients.[30] Chemotherapy regimens associated with an increased risk for IFD included intensive induction timing versus standard timing associated with the AML protocol CCG2891[20] and relapse versus front line therapy in children with AML[19], while reduced intensity conditioning was associated with an increased risk of IFD in allogeneic HSCT recipients.[13]

 GVHD was commonly identified as a risk factor for IFD, with four HSCT studies finding a significant association with severe acute GVHD[10,12,17,29] and three studies associating IFD with chronic GVHD.[12,14,17,29]In these studies, severe GVHD was inclusive of grade II and higher[10,17,29] or grade III and higher.[12] Finally, increasing age was identified as a risk factor for IFD in both HSCT and cancer populations. Age was dichotomized at a threshold of 7.5 and 10 years in one[13] and three[15,18,20] studies, respectively. In each of these studies the older age group had increased risk for IFD.

 In the studies that focused on fever and neutropenia episodes, significant risk factors for IFD were fever on day 4 of neutropenia, acute monocyte count (AMC) < 100/ μL on day 4 and C-reactive protein greater than or equal to 9.0 mg/dL on day 4 of the fever, neutropenia greater than 30 days in duration, and days in the hospital.[24-26,30]

DISCUSSION

 This systematic review identified 22 studies that investigated risk factors for IFD in at-risk pediatric patients. These studies were heterogeneous relative to the patient population studied and included HSCT recipients as well as children with cancer. The studies also focused on risk at different clinical time points and assessed various potential risk factors with varying methods of measurement of each factor. This heterogeneity prohibited an analysis that would combine data across studies. Nonetheless, this systematic review confirmed a number of risk factors often associated with IFD and provides a more granular understanding of these risk factors. Further, additional factors not typically associated with IFD risk, such as age, were also identified.

 As might be expected, neutropenia duration was the most commonly identified risk factor for IFD. Some of the analyses considered neutropenia as a continuous variable and as such were able to show that each day of increased neutropenia duration had a corresponding increased risk for IFD. Thresholds for 28 and 30 days of neutropenia were associated with increased risk for IFD in two different studies. However, these thresholds appear to have been arbitrarily chosen for analyses and it is not clear if such risk would have been present at lower thresholds.[15,30] Johnston et al. did examine two different thresholds for neutropenia, 10 days and 15 days.[1] The former was not statistically significantly associated with IFD while the latter was. These data suggest that the risk for IFD from neutropenia for children significantly increases at some point beyond 10 days duration, although the threshold likely also varies depending on concurrent other risk factors. Similarly, the adult published clinical practice guideline for neutropenia denote high risk IFD status after 10 -15 days of neutropenia.[32] This was based on published adult data linking an increased risk of invasive aspergillosis to neutropenia durations of at least 10 to 15 days.[33] It is important to note that lymphopenia was not assessed as a risk factor for IFD in the identified pediatric studies for this systematic review. Lymphopenia has been identified as a risk factor for IFD in adult HSCT recipients.[34] Future investigation regarding the impact of lymphopenia on the risk of IFD in children is needed.

 Depth of neutropenia is also an important component of the neutropenia risk profile for IFD. An ANC < 100 μL prior to IFD onset, and specifically an AMC < 100 μL during an episode of fever and neutropenia, were each associated with an increased risk of IFD. As both depth and duration of neutropenia were separately identified as a risk factor for IFD, it is intriguing to consider a single measure that would consider these elements simultaneously. The D-index is a measure that combines both depth and duration of neutropenia in a single assessment and has been linked to an increased risk for IFD.[35] However, this measure has only been derived in a small case-control study and was not investigated in any of the studies comprising this systematic analysis. Future investigation of the D-index as a mechanism to stratify patients by risk of IFD should be considered.

 High dose steroid exposure was frequently identified as an independent risk factor for IFD both in HSCT and cancer patients. However, it is notable that each study defined their threshold for high dose steroid exposure in varying ways, including 1 mg/kg/day of prednisolone for more than 1 week,[11] 2 mg/kg/day of prednisolone for 10 or more days,[15] 0.25 to 1 gram/day of methylprednisolone for 5 days followed by 2mg/kg/day of prednisolone,[17] or 10mg/m2  of dexamethasone.[1] This variation precludes an ability to define a single dosing regimen for labeling someone as receiving high dose steroids.

 A number of baseline clinical factors such as a diagnosis of AML, high risk or relapsed ALL, or allogeneic HSCT were confirmed as risk factors for IFD. Additionally, those children undergoing HSCT for severe aplastic anemia or Fanconi anemia had an increased risk for IFD.[15] Expectedly, intensive timing versus standard timing chemotherapy for AML[20] was associated with an increased IFD risk but suprisingly reduced intensity conditioning for HSCT conferred an increased risk for IFD.[13] This increased risk with reduced intensity conditioning was only found in one study and needs further investigation to confirm these findings. Finally, both severe acute and chronic GVHD were associated with IFD risk across a number of studies.[10,12,14,17,29] Age was the only demographic factor implicated in IFD risk across multiple studies. Increasing age correlated with increased IFD risk. Identified age threshold for IFD risk included 7.5 years[13] and10 years[15,18,20] of age. However, it is unclear if an association with IFD would have been identified at a lower age threshold. Age is not frequently a metric utilized for defining risk for IFD in children but these data suggest that moving forward, age should be considered in risk stratification. It is not clear whether age itself is a risk factor or rather a proxy for other factors such as chemotherapeutic or conditioning treatment intensity, altered pharmacokinetics, obesity or associated co-morbidities such as hyperglycemia.

 While this study was successful at identifying individual risk factors for IFD, there was a notable absence of any published prediction rules leveraging multiple factors simultaneously or in sequence to stratify patients into risk categories. The development of prediction rules has been successful for risk stratification regarding bacterial infections.[36-39] Similar prediction rules for IFD would be clinically useful to inform targeted prophylactic and empiric antifungal therapy strategies. In the interim, we can only use the single risk factors to help guide IFD risk stratification measures in clinical practice guidelines.

 The primary strength of this review is its rigorous and systematic approach to identify, screen and include publications of all languages to ensure that all available published studies informed the identification of risk factors for IFD in children with cancer or HSCT. This has not previously been done for this patient population in spite of the importance for establishing a systematic platform for pediatric IFD risk stratification that can be used to inform clinical management strategies. However, this review must be interpreted in light of its limitations. First, the outcome of IFD for this systematic review was inclusive of a heterogeneous group of fungal pathogens presenting across a range of patient groups. Certain risk factors may be more or less important depending on the clinical scenario (i.e. HSCT or leukemia) and dependent on the pathogen of concern (i.e. *Candida* species or invasive mold). However, the primary goal of this endeavor was to systematically identify risk factors that pediatric clinicians can leverage as general guides to increase or decrease their suspicion of IFD when caring for pediatric HSCT recipients and cancer patients. Second, publication bias is difficult to test in this setting and, thus, it is unknown if or how many negative studies were performed but not published. Third, risk for bias was assessed in each included study relative to patient selection, confounding, and analytic plan (Table 2). In a number of studies the risk of bias for one or more of these parameters was high and this needs to be considered when assessing whether an identified factor or factors are truly associated with an increased risk for IFD. For example the risk of bias related to confounding was high in three of the studies that found a significant association between acute GVHD and IFD (Table 2) suggesting that this may not be an independent association. Finally, we only considered risk factors that were shown to be statistically significantly associated with IFD in the studied population. This approach does not take into account the study’s power and thus there is an opportunity for identifying spurious associations or missing clinically meaningful associations. Some of the risk factors were identified in univariate analysis without consideration for confounding by, or collinearity with other covariates.

 In conclusion, this systematic review summarizes individual risk factors identified in publications since 1980. In many instances, this study confirms factors that are routinely considered in daily clinical practice. Children receiving an allogeneic HSCT and those receiving chemotherapy for AML and high risk or relapsed ALL should be considered high-risk for IFD. Among these groups HSCT patients with preceding Fanconi anemia or severe aplastic anemia as well as AML patients receiving intensive therapy are at particularly increased risk. Additionally, patients with neutropenia longer than 10 days and those receiving high dose corticosteroids should be considered high risk for IFD. Other factors such as increasing age are not routinely included in pediatric risk assessment but should be considered. Future efforts should focus on defining more precisely thresholds for a particular risk factor (i.e. age, neutropenia duration) and on development of prediction rules inclusive of individual factors to further refine risk prediction. Additional investigation of other potential predisposing factors such as genetic variation is needed in large pediatric cohorts with well-defined measurement of IFD.

**Conflicts of Interest:**

B. T. F. has received research support from Pfizer, Merck and Aunsun Biopharma. W. J. S. has received research funding from and been a consultant to Merck & Co. and Astellas Pharma. T.L. has been a consultant for Astellas Pharma, Gilead Sciences, and Merck T. E. Z. has been a consultant to Merck & Co., Astellas Pharma, Pfizer, and Cubist, has received research funding from Merck and Cubist, and received payment for development of a Terranova CME presentation.

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Figure 1 Legend:

Title: Flow Of Study Publication Identification and Selection Process

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