

## Rationale for Use of Prophylactic Antifungal Therapy in Pediatric Patients with Leukemia and Hematopoietic Stem Cell Transplantation

Surekha Tony<sup>1\*</sup>, Tony John<sup>2</sup> and Roshan Mevada<sup>3</sup>

<sup>1</sup>Pediatric Hematology/Oncology/BMT Unit, Department of Child Health, Sultan Qaboos University Hospital, Oman

<sup>2</sup>Jawaharlal Nehru Medical College, Belgaum, India

<sup>3</sup>Father Muller Medical College, Mangalore, India

**\*Corresponding Author:** Surekha Tony, Pediatric Hematology/Oncology/BMT Unit, Department of Child Health, Sultan Qaboos University Hospital, Oman.

**Received:** April 14, 2021; **Published:** April 23, 2021

### Abstract

Invasive fungal infections (IFIs) are an important concern in immunocompromised patients with high morbidity and mortality and treatment of these infections can be difficult once established. The significance of prevention cannot be overemphasized.

Although approaches include preventing exposure through environmental strategies (e.g. high efficient particulate air filters), preventing disease with the use of antifungal prophylaxis remains of high significance.

**Keywords:** *Invasive Fungal Infections; Immunocompromised; Children; Antifungal Prophylaxis*

Although therapeutically effective, chemotherapy can cause toxicities in pediatric patients; with neutropenia posing an increased risk of invasive fungal infection (IFI). Factors other than neutropenia contributing to the risk of IFI include lymphopenia (corticosteroid therapy, anti-T-cell cytotoxic agents), decrease in phagocytes and monocytes (myelosuppressive therapy) and muco-cutaneous breach (indwelling catheters, mucositis) [1].

Establishing the diagnosis of IFI in pediatric patients with hematological malignancies is often sort with difficulty and outcome is dismal if treatment is delayed.

Clinical features are often non-specific and microbiological cultures are usually negative. Histopathological diagnosis requires invasive procedures to obtain specimens, which is often impaired for grave conditions in severely immunosuppressed patients. [2].

Galactomannan (GM) and  $\beta$ -D-glucan are non-invasive assays used to diagnose IFI. GM is a heteropolysaccharide present in the cell wall of *Aspergillus* spp, and  $\beta$ -D-glucan is a cell wall polymer found in fungi with the exception of *Cryptococcus* spp. and *Zygomycetes*.

However, studies have shown that the roles of GM and  $\beta$ -D-glucan testing in diagnosing IFI in pediatric patients is limited.

Pediatric patients at increased risk of developing an IFI include those receiving chemotherapy for hematological malignancies including acute myeloid leukemia (AML), relapsed acute lymphoblastic leukemia (ALL) and severe aplastic anemia (SAA) and those undergoing Hematopoietic Stem-Cell Transplant (HSCT) [4].

Studies have reported a 1-year incidence of IFI in pediatric HSCT patients to be as high as 13 - 20% with a 58 - 83% mortality [5,6].

*Candida* spp. and *Aspergillus* spp are the most common organisms identified post HSCT [7]. Neutropenia following HSCT is known to be associated with candida spp. infection. Dvorack., *et al.* have reported that *Aspergillus* spp. tends to have a bimodal distribution, with a first peak at a median of 16 days and the second at a median of 96 days post-allogeneic HSCT [1].

Burgos., *et al.* reported death in 53% of children diagnosed with invasive aspergillosis, and a higher fatality rate of 78% in patients with allogeneic hematopoietic cell transplant (HSCT) [4].

Several studies have reported a high incidence (up to 29%) of IFI in pediatric patients with both newly diagnosed and relapsed AML [8,9].

On the other hand, the incidence of IFI in ALL is higher only in relapsed patients, suggesting the need for prophylaxis in them [10].

In patients with SAA, mortality due to IFI is reported to be 11% [5]. Neutropenia in SAA is a major contributing factor for higher rate of colonization which can result in IFI during HSCT in these patients.

Based on current evidence, we recommend antifungal prophylaxis in pediatric patients receiving treatment for newly diagnosed and relapsed AML, relapsed ALL, SAA and those undergoing HSCT. There is no evidence to justify the routine use of prophylactic antifungals in patients with newly diagnosed ALL.

Early diagnosis of IFI in pediatric patients with malignancies remains a challenge and further research for non-invasive tests is crucial. Despite the availability of newer antifungal agents, IFI are often difficult to treat with increased risk of mortality.

To conclude, in order to improve the outcome of pediatric patients with malignancies, it is noteworthy to adopt an approach of prevention to IFI by adhering to guidelines for antifungal prophylaxis. Besides improving overall survival and avoiding morbidity, it is a cost-effective approach in the management of such immunocompromised patients.

### Declarations

The authors declare that there was no funding support and have no conflicts of interest relevant to this article to disclose.

### Authors Contribution

S Tony took part in conceptualization and design of the study, collection of data, critical literature review, and drafting of the manuscript; T John took part in conceptualization of the study, critical literature review and drafting of the manuscript. R Mevada took part in conceptualization of the study, critical literature review and drafting of the manuscript. All authors agreed upon the final version of the manuscript. All authors have reviewed and agreed upon the manuscript content.

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**Volume 10 Issue 5 May 2021**

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