EDITORIAL

Invasive Candidiasis in Children: Challenges Remain

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Invasive fungal infections (IFIs) are increasingly reported among critically ill children admitted to pediatric intensive care unit (PICU), and they also pose unique challenges in diagnosis and management. The incidence of IFIs has increased steadily over the last few years, necessarily due to increase in the prevalence of susceptible hosts, more specifically children with hematological malignancies, congenital and acquired immunodeficiency syndromes, and recipients of hematopoietic stem cell/solid organ transplants. Also, improved survival of children with debilitated illnesses who are chronically dependent on life-sustaining technologies, increased use of invasive procedures such as central venous catheters (CVCs), parenteral nutrition, and prolonged use of broad-spectrum antibiotics has contributed to the increase in IFIs in these children.

Diagnosis of IFIs in children is challenging, owing to the nonspecific clinical signs and symptoms, low yield of culture-based methods, and the lack of widespread access to validated biomarkers in children. This underlines the importance of epidemiologic studies on IFIs in children admitted to PICU, to understand the specific risk factors that are relevant in our settings. This would help in identifying at-risk children and initiate appropriate strategies to diagnose and treat IFIs early. *Candida* is the leading cause for IFIs in hospitalized children with an incidence varying between 1.9 and 10 per 100,000.[1] In general, the incidence is higher in neonates and infants, and higher incidence is also reported in children undergoing cardiothoracic surgery for congenital heart diseases.[2,3]

Various risk prediction models have been developed for predicting invasive candidiasis (IC) among hospitalized patients. Potentially modifiable risk factors include the presence of endotracheal tube, CVC, use of antibiotics, and use of intravenous lipid emulsion.[4] Candida score is another commonly employed risk prediction model that comprises of use of parenteral nutrition, surgery, multifocal colonization, severe sepsis as the parameters, and a score of ≥3 is taken as a positive cutoff.[5] Such risk prediction models can be used as a guide at bedside, in identifying high-risk group patients for early initiation of antifungal therapy. One of the major practical problems with such a "risk prediction model" approach is that they fare best when our population cohort is similar to the original derivation cohort. Variations in the clinical characteristics, underlying predisposing factors, and colonizing *Candida* species will affect the performance of the score. Also, most of the models have a high negative-predictive value and hence can be useful to identify those who are less likely to need antifungal therapy.[6]

In the current issue of IJCCM, Rajeshwari et al. have attempted to identify the predisposing risk factors of invasive Candida infection and their outcomes in their PICU.[7] Invasive candidiasis cases were selected based on retrospective analysis of the clinical and microbiologic data and isolation of *Candida* species in blood, endotracheal aspirates, urine, and pus along with clinical symptoms. *Candida tropicalis* was the commonest species isolated in the present cohort, accounting for nearly 50% of IC. Ventilator-associated pneumonia (VAP) was the predominant fungal infection that was detected in the current study. The authors have included children with clinical suspicion of VAP in their case inclusion; however, the isolation of *Candida* species in endotracheal secretions and attribution of their causative role need to be taken with a pinch of salt. It has been observed that *Candida* colonizes the tracheobronchial tree in close to 20% of intubated patients within the first few days, and this proportion increases with the duration of mechanical ventilation.[8] Differentiating colonizer from invasive infection is difficult, and histologic demonstration of fungus in the lung tissue along with inflammatory changes is the only widely accepted criterion for the diagnosis of Candida pneumonia.[9] A few patients in the present cohort had *Candida* isolated at other sites as well, pointing toward multifocal fungal colonization. There is a positive correlation noted between colonization of fungus and subsequent candidemia among PICU patients, regardless of the site of colonization.[10] In children with candidemia, secondary Candida pneumonia could happen through hematogenous seeding. Primary Candida pneumonia is rare and needs tissue diagnosis which is rarely performed in the clinical settings.[11,12]

This takes us to the intrinsic difficulty in proving fungal infections in children, since reliance is on cultures which is not only time-consuming, but also less yielding. Many of the biomarkers that are in use in adults have not been validated in children. So, reliance on cultures alone would miss the crucial window of opportunity where early antifungal administration would be life-saving in these children with IFIs. Unlike other predisposing conditions such as neutropenia, post-transplant setting, where fungal infections are upfront considered and evaluated, risk factors for IFIs in previously healthy children admitted to PICU are bound to be overlooked. The

authors have concluded that neutropenia, mechanical ventilation, presence of CVC, antibiotic duration >5 days, peritoneal dialysis, and amino acid administration are independent risk factors for candida infection.[7] Among these, peritoneal dialysis as a risk factor is particularly relevant to low- and middle-income countries (LMICs) where this modality of renal replacement therapy is often resorted to, especially in neonates and infants.

This study also reiterates the increasing prevalence of Non-albicans Candida (NAC) in our ICUs, which pose greater challenge in LMICs due to the need for more expensive treatment options. Attributable mortality risk due to IC and NAC could not be obtained from the current study; however, it is important to note that six children succumbed prior to the availability of culture results, which we have to rely upon in the real-life scenario for diagnosis of IFIs.

The need of the hour is to develop reliable biomarkers with lesser turnaround time, that can help in initiating preemptive antifungal therapy in high-risk children admitted to PICU. In a recent multicenter prospective study on the use of biomarkers for diagnosis of IC, authors have concluded that T2Candida testing was most sensitive for rapid detection of *Candida* species in children with suspected IC.[13] Risk stratification based on the available epidemiologic knowledge on IFIs combined with use of biomarkers would help us to identify those who would benefit from antifungal treatment, and at the same time, avoid unnecessary antifungal exposure to others deemed to be at lesser risk for IFIs. Epidemiologic studies similar to the current one will add to our existing knowledge gap in this topic and be relevant to plan future studies to test such biomarkers and implement targeted interventions.

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