Invasive Fungal Infections in the Pediatric Intensive Care Unit

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Invasive fungal infections (IFIs) are a heterogeneous group of yeast and mold infections that are particularly relevant to immunocompromised children with hematologic malignancies, hematopoietic stem cell transplant (HSCT) and solid organ transplant recipients, but are also increasingly recognized in debilitated children requiring prolonged Pediatric Intensive Care Unit (PICU) support for any medical or surgical reason. PICU admission by itself is a significant risk factor for development of an IFI, but the risk is determined by the interaction of host predisposition and environmental exposure.

Epidemiologic data for IFIs in critically ill children are scarce, making extrapolation of adult studies in children inevitable. However, children differ compared with adults when it comes to IFIs. They have less underlying comorbidities, have major differences in the pharmacokinetics of some commonly used antifungals and finally most of the nonculture-based diagnostics have not been adequately validated in children, that is, their optimal thresholds for positivity are unknown.

The clinical signs and symptoms of IFIs are quite nonspecific, invasive disease is difficult to distinguish from colonization and available diagnostic tests are imperfect. Blood cultures have low sensitivity, polymerase chain reaction of fungal DNA, which albeit highly accurate lacks standardization and has low commercial applicability, and galactomannan (GM) is useful only for Aspergillus spp. with many false-positive results and limited experience in noncologic settings. Measurement of serum or plasma (1→3)-β-D-glucan (BDG), a component of the cell wall of most fungi except Zygomycetes and cryptococci, has been applied as a serial panfungal screening procedure for distinguishing proven or probable IFIs from no IFIs in high-risk patients. A meta-analysis showed the pooled sensitivity of BDG to be 76.8%, and the specificity 85.3%, but only 1 of the 16 analyzed studies included critically ill children. Therefore, currently BDG testing is not recommended to guide clinical decision-making in children. Serum procalcitonin, which has been shown to correctly discriminate between systemic bacterial infection and noninfectious inflammatory conditions, is consistently lower in IFIs compared with bacterial sepsis, but the diagnostic value of this observation in clinical practice needs further testing.2

**CANDIDA INFECTIONS**

Candidiasis is the leading IFI in hospitalized children, and depending on the medical center is the third or fourth most common hematogenous infection.3 A declining trend has been recently noted in the incidence of pediatric candidemia in North America because of the implementation of guidelines that emphasize application of maximum barrier precautions during line placement, strict hand hygiene, aseptic dressing changes, use of >0.5% chlorhexidine with alcohol for skin preparation, appropriate site selection for line placement (avoidance of femoral placement if possible) and daily review of catheter necessity.

Only 5 Candida species (Candida albicans, Candida parapsilosis, Candida glabrata, Candida tropicalis and Candida krusei) cause the majority of all candidemia episodes in children. Although C. albicans remains the single most common species, over the last 30 years a decrease in infections due to C. albicans and an increase in infections due to nonalbicans Candida species have been noticed. Nowadays, C. parapsilosis has emerged as a frequent pathogen of bloodstream infections in infants with central venous catheters (CVCs), who receive total parenteral nutrition, and has exceeded C. albicans as the most common cause of candidemia in several units worldwide.

Typical pediatric patients at risk for candidemia in the PICU are those with cancer or a chronic neurologic, respiratory or gastrointestinal illness that are on mechanical ventilation, especially if they receive long courses of broad-spectrum antibiotics. In the PICU, candidemia most commonly presents

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**References:**
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molecular diagnostics. 7

Candida spp. by combining magnetic resonance with

treatment of candidemia. A clinical prediction model

to multiple body sites is an independent predictor

ill children who eventually develop candidemia are colonized with the same

candidemia of having various combinations

In critically ill children, CVCs should be removed as early

catheters being associated with the highest

critically iii children and adults is a very

invasive candidiasis. Children with HIV

Children at risk. A retrospective cohort study

Aspergillus fumigatus is the most

Invasive Fungal Infections

Table 1. Preferred Antifungal Therapy for the Most Common IFIs in Critically Ill Children

<table>
<thead>
<tr>
<th>IFIs</th>
<th>Primary Therapy</th>
<th>Alternate Therapy</th>
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<tbody>
<tr>
<td>Candidemia in nonneutropenic children*</td>
<td>Echinocandins †&lt;br&gt;Caspofungin: loading dose 70mg/m² IV, then 50mg/m² IV daily&lt;br&gt;Micafungin: 2–4 mg/kg/d IV, doses ≥10 mg/kg/d IV are needed in neonates</td>
<td>Fluconazole (loading dose 12mg/kg IV or oral, then 6mg/kg IV or oral), lipid formulations of amphotericin B (3–5mg/kg/d), voriconazole (loading dose 6mg/kg IV twice daily for 2 doses, then 3mg/kg IV twice daily)</td>
</tr>
<tr>
<td>Candidemia in neutropenic children*</td>
<td>Echinocandins †&lt;br&gt; (doses as above)</td>
<td>Lipid formulations of amphotericin B, fluconazole (in stable patients with susceptible isolates) and voriconazole (if additional mold coverage is desired; doses as above)</td>
</tr>
<tr>
<td>Invasive aspergillosis</td>
<td>Voriconazole (loading dose 9mg/kg IV twice daily for 2 doses, then 8mg/kg IV twice daily)</td>
<td>Liposomal amphotericin B (3–5mg/kg/d), other lipid formulations of amphotericin B (ABLC 5mg/kg/d IV), voriconazole + echinocandins (in selected patients)</td>
</tr>
<tr>
<td>Mucormycosis (zygomycosis)</td>
<td>Liposomal amphotericin B (5mg/kg/d), other lipid formulations of amphotericin B (ABLC 5mg/kg/d IV)</td>
<td>Posaconazole (safety and efficacy not established in patients &lt;18 years of age)</td>
</tr>
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</table>

*Testing for azole susceptibility is recommended for all bloodstream Candida isolates.
†Caspofungin and micafungin approved for pediatric use. Anidulafungin not yet approved for pediatric use. Anidulafungin at 1.5mg/kg/d is suggested by the Infectious Diseases Society of America for use in neonates and children. ABLC indicates amphotericin B lipid complex.

aspirellus infections

Invasive aspergillosis (IA), an infection associated with high mortality, has increased in recent decades due to increases in the number of immunocompromised children at risk. A retrospective cohort study using a US national database of pediatric hospital inpatient stays estimated an annual incidence of 0.4% in 2000.10 Children with malignancy accounted for 74% of the cases. The highest incidence of IA was seen in children who had undergone allogeneic bone marrow transplantation (4.5%) and those with acute myelogenous leukemia (4%). In these 2 settings, IA is more common than invasive candidiasis. Children with HIV infection and chronic granulomatous disease are further populations at risk of IA.

Aspergillus fumigatus is the most common cause of IA worldwide, followed by Aspergillus flavus, Aspergillus niger and Aspergillus terreus with substantial variation by site. Aspergillus spp. are primarily airborne pathogens and, hence, most cases of IA involve the respiratory tract. In the largest retrospective review of contemporary cases of proven and probable pediatric IA, the most common clinical site was the lungs and the most frequent diagnostic radiologic finding was nodules.11 Unlike adults, only 2.2% of children showed the air crescent sign, 11% demonstrated the halo sign and cavitation was seen in 24.5% of patients. These differences compared with adults may have a major impact on timely diagnosis of this serious infection in children.

Critically ill children may contract aspergillosis before or during their hospitalization in the PICU. Construction or renovation adjacent to areas housing immunocompromised children and housing HSCT recipients in nonlaminar air flow rooms are known risk factors for IA. Damaged skin and gut are further portals of entry of Aspergillus spp. Central nervous system dissemination is a serious complication of IA with high
fatality that has improved in recent years with aggressive surgical treatment. Children with acute myelogenous leukemia who remain deeply neutropenic for several weeks during remission-induction chemotherapy, as well as children with high-risk acute lymphoblastic leukemia, relapsed leukemia and aplastic anemia, are at high risk for IA and are the usual patients with IA hospitalized in PICUs. In these patients, colony-stimulating factors should strongly be considered, as a means of alleviating the duration of neutropenia. Administration of high-dose corticosteroids (≥22 mg/kg/d) for extended periods, as a means of combating graft versus host disease, places transplanted children at very high risk of IA.

Serial computed tomography scans of the chest and sinuses are the basis for detection of IA. Obtaining a histologic diagnosis is frequently impossible due to the invasive nature of the procedures required in critically ill, neutropenic, thrombocytopenic and unstable patients. A systematic literature review of the diagnostic yield and complication rates of bronchoalveolar lavage (BAL) and lung biopsy in the evaluation of pulmonary lesions in patients with cancer and HSCT recipients showed that an infectious diagnosis was more commonly made with BAL, while complications and procedure-related mortality was 4-fold higher for lung biopsy. Unfortunately, respiratory insufficiency and bleeding refractory to platelet transfusion may preclude BAL.

Infection by *Aspergillus* can be detected by using a commercially available enzyme immunoassay for GM in serum and/or BAL, but results are dependent on the reference standard definitions. Serial measures of GM with this assay during periods of neutropenia in critically ill children, as well as more pharmacokinetic and efficacy data of newer antifungals, are urgently needed.

**OTHER IFIS**

Mucormycosis is the second most common cause of invasive mold infection in the PICU, shares similar risk factors and presentation with IA, but in addition is uniquely associated with poorly controlled diabetes mellitus. Immune reconstitution, aggressive surgery and active antifungal therapy are vital for survival. Recently, isavuconazole, a newer broad-spectrum triazole has been shown to have comparable efficacy to amphotericin B against mucormycosis, but has not yet been approved for infants and children.

In conclusion, IFIs are increasingly recognized in critically ill children. Although they have been studied primarily in severely immunocompromised children, they can affect debilitated children who require long-term intensive care for any reason. The development of nonculture-based serologic and molecular diagnostic techniques is promising but has not been adequately validated in pediatric critically ill patients, especially nononcologic children. Prospective pediatric-only testing of nonculture-based diagnostic assays in well-defined subpopulations of critically ill children, as well as more pharmacokinetic and efficacy data of newer antifungals, are urgently needed.

**REFERENCES**


