Invasive Fungal Infections in the Pediatric Intensive Care Unit

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Invasive fungal infections (IFIs) are a heterogenous 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 nononcologic 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.[1] 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

Candidemia 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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with refractory fever or a new episode of fever despite use of antibiotics. In critically ill children, the incidence rate of candidemia varies from 1.9 to 10 per 100,000, with comparable 30-day mortality with that of bacterial sepsis/septic shock. Candidemia is more frequent in neonates and young infants with underlying congenital heart diseases. Prophylactic use of fluconazole in carefully selected high-risk neonates has been shown to decrease the risk of candidemia.[4]

The individual prediction of candidemia in critically ill children is a very difficult challenge, although many well-established risk factors exist. These include prematurity, prolonged mechanical ventilation, use of central lines and urinary catheters, administration of parenteral nutrition or of intralipid agents, malignancy, neutropenia, neurologic disease, use of corticosteroids and broad-spectrum antibiotics, gut surgery and hemodialysis. The majority of critically ill children who eventually develop candidemia are colonized with the same *Candida* spp., and the presence of colonization at multiple body sites is an independent predictor of candidemia. A clinical prediction model of candidemia for critically ill children was developed at Children's Hospital of Philadelphia in 2010.[5] Predicted probabilities for candidemia of having various combinations of established risk factors ranged from 10.7% to 46%, but these results were not confirmed in an international multicenter setting.[6]

Blood cultures are the gold standard for diagnosis of candidemia but are positive in a minority of cases and often with a long delay in the course of infection. Newer techniques, such as the T2Candida panel, provide fast species-specific detection of *Candida* spp. by combining magnetic resonance with molecular diagnostics.[7]

CVCs play an important role in pediatric candidemia, with silastic percutaneous catheters being associated with the highest rates of hematogenous infection. In septic children, CVCs should be removed as early as possible in the course of candidemia.

Echinocandins that are fungicidal against *Candida* spp. and highly active against *Candida* biofilms are recently recommended by the European Society of Clinical Microbiology and Infectious Diseases, the Infectious Diseases Society of America and the European Conference on Infections in Leukemia as first line agents in the treatment of candidemia in children and adults (Table 1). All 3 echinocandins have minimal side effects and can achieve therapeutic drug concentrations in all sites except the central nervous system, eye and urine. Fluconazole or voriconazole is appropriate for children with candidemia due to azole-susceptible isolates, but have the disadvantage of numerous drug interactions. Major differences exist in the pharmacokinetics of azoles in children versus adults. For example, fluconazole is rapidly cleared necessitating a higher daily dose of 12 mg/kg. Serious and potentially life-threatening interactions between azoles (itraconazole, voriconazole and posaconazole) and vincristine, a commonly used drug in children with acute lymphoblastic leukemia, have been described and include peripheral and autonomic neuropathy, seizures, hyponatremia and gastrointestinal toxicity. Hence, an alternative antifungal should be used in such cases.[8] Therapeutic drug monitoring is increasingly used to guide therapy with azoles and has shown that frequently critically ill children achieve subtherapeutic blood levels with current dosing recommendations.[9] Nevertheless, the ultimate impact of therapeutic drug monitoring on clinical care of critically ill children requires further testing.

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

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

*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 1.5 mg/kg/d is suggested by the Infectious Diseases Society of America for use in neonates and children.

ABLC indicates amphotericin B lipid complex.

ASPERGILLUS 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 (≥2 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.[12] 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.[13] Serial measures of GM with this assay during periods of prolonged neutropenia or active graft versus host disease in patients at risk may lead to an early, noninvasive diagnosis of IA before the time lesions are visible on computed tomography scans. Although some studies show lower sensitivity and specificity in children compared with adults, a study of 64 pediatric HSCT recipients showed 98.4% specificity by sample and 91.4% by patient.[14] Aspergillus polymerase chain reaction in BAL fluid has similar sensitivity and specificity and comparable utility with BAL GM.

Voriconazole is the treatment of choice for IA in children, but higher dosages are required in pediatric patients to achieve similar exposures with adults (Table 1). Amphotericin B deoxycholate and its lipid derivatives are appropriate, when voriconazole cannot be administered. Echinocandins are effective as salvage therapy, but should not be used as monotherapy for the primary treatment of IA.

OTHER IFIS

Mucormycosis is the second most common cause of invasive mould 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.

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