Invasive Fungal Infections in Children

Hans Jürgen Dornbusch, MD,* Paolo Manzoni, MD,† Emmanuel Rolilides, MD, PhD,‡ Thomas J. Walsh, MD,§ and Andreas H. Groll, MD¶

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The past two decades have seen a considerable increase in both frequency and importance of opportunistic invasive fungal infections in pediatric hospitals. At the same time, major advances have been made in the diagnosis of fungal diseases, the development of algorithms of antifungal interventions, and the design and implementation of pediatric clinical trials. Most importantly, several new antifungal agents have entered clinical practice with the result that antifungal therapy has become safer, more effective, but also more complicated.1,2 This article reviews the current epidemiology of invasive fungal infections in pediatric patients, new emerging diagnostic modalities and concepts for their treatment and prevention.

CURRENT EPIDEMIOLOGY

Invasive fungal infections (IFIs) occur in neonates and children with compromised immune system or in critical condition. These include premature neonates, patients in pediatric intensive care units, with implants and burns, with congenital immunodeficiencies, neutropenia, hematopoietic stem cell transplantation (HSCT), solid organ transplantation, HIV infection and treated with immunosuppressants. Infections in these patients are due to Candida spp., Aspergillus spp., Cryptococcus spp. and other, less frequent opportunistic fungi.

Invasive Candidiasis (IC)

Candida spp. are the fourth most common isolate and is associated with the second highest case fatality rate in children with bloodstream infections. The spectrum of IC ranges from catheter-associated candidemia to single organ and disseminated infection with or without candidemia. Risk factors for candidemia are the presence of a central venous line, neutropenia, use of immunosuppressants and, in neonates, low gestational age, fungal colonization, high glucose levels, antibiotic and H2-blocker use.3 The most frequently affected organs in children with disseminated candidiasis are lungs, liver, kidney and brain. The frequency of IC is greater in children than in adults and is particularly high in neonates (47 vs. 30 vs. 150/100,000 admissions, respectively).4,5 The frequency of neonatal candidiasis increases with decreasing birth weight: up to 12–15% in extremely low birth weight (ELBW) infants.6 C. albicans is the most common invasive Candida spp. in pediatric patients, accounting for 53% of cases. C. parapsilosis (21%) and C. tropicalis (10%) are the most prevalent non-C. albicans spp., whereas C. glabrata and C. krusei are infrequent. The attributable mortality of IC has been estimated to be 10% vs. 15–38% in adults.4,5 Mortality of C. parapsilosis is lower than that for other Candida spp. Children with IC have longer stays in hospital causing greater costs as compared to patients without IC.

Invasive Aspergillosis (IA)

Most children with invasive aspergillosis present with pulmonary aspergillosis; dissemination to other sites, particularly to the CNS, also occurs. Sinusitis and primary cutaneous or gastrointestinal aspergillosis are unusual. A. fumigatus is the most common cause of IA followed by A. flavus and A. terreus. Incidence rates for aspergillosis by underlying disease are similar in children and adults.7 In two large series,7,8 the most common underlying condition was malignancy (74 and 63%) with highest incidences in patients with acute myeloid leukemia and allogenic HSCT. The case fatality was 53%, and multivariate analysis showed that allogeneic HSCT was a predictor of poor prognosis. In patients with chronic granulomatous disease, 1A affects approximately 30% and is characterized by higher frequency of A. nidaus (particularly associated with bone infections) and lack of angioinvasion.
Infections by Less Common Fungi

Zygomycetes are mostly airborne and require breakdown of phagocytic functions or protective surfaces. In a review of 157 pediatric cases of zygomycosis, most patients presented with cutaneous (27%) or gastrointestinal (21%) disease, followed by rhinocerebral (18%) and pulmonary (16%) disease. Among 59 reported cases of neonatal zygomycosis, 77% occurred in premature infants. Gastrointestinal (54%) and cutaneous (36%) disease were more frequent than in older patients. Rates of disseminated disease (56%) and mortality (64%) were exceedingly high, indicating that zygomycosis is associated with a particularly poor prognosis in neonates. Fusarium has emerged as the second most common filamentous pathogen after Aspergillus in some institutions. Fusarium infections may be similar to IA, but frequently present with fungemia and disseminated skin and soft tissue lesions. Infection due to Trichosporon asahii in neutropenic patients and neonates mimic IC with fungemia and disseminated infection; mortality is high. Cryptococcosis appears to be an infrequent opportunistic infection; in HIV-infected children, the estimated 10-year prevalence is 1%.13

ADVANCES IN EARLY DIAGNOSIS

Successful management of IFIs relies on early recognition and rapid initiation of effective treatment. In view of the increasing diversity of fungal pathogens in high risk patients, the differences in the antifungal spectrum of the available agents, and the looming threat of resistance, identification of the infecting isolate at the species level and information on drug resistance are important in order to provide state of the art patient care. Microscopy and culture of appropriate specimens remain the gold standard of mycological diagnosis, despite difficulties in obtaining appropriate and/or sufficient specimens, long time of culturing and negative results. Modern imaging studies, detection of circulating fungal cell wall components and DNA in blood and other body fluids may enhance the laboratory diagnosis of IFIs.14

Imaging Studies

In neutropenic adults, serial high-resolution computed tomography (HRCT) imaging has been shown to positively impact on early diagnosis and outcome of invasive pulmonary aspergillosis. However, there is growing recognition that CT findings characteristic in adults, such as the “halo” and “air crescent” signs, are rather infrequent in pediatric patients with pulmonary aspergillosis7,16 for reasons that are not entirely clear. Thus, in immunocompromised pediatric patients at risk, any radiological finding needs to be considered to represent invasive pulmonary mold infection and should prompt further evaluation. Routine serial CT imaging in children carries a risk of radiation exposure that is proportionally greater than that of adults. Hepatosplenic candidiasis can be detected early by ultrasound or MRI. MRI is useful to investigate other sites and to guide diagnostic and surgical interventions.18

Detection of Cell Wall Markers

Based on their performance in adults, two detection methods have been included in the MSG/EORTC diagnostic criteria developed for clinical research. The galactomannan antigen ELISA (Platelia® Aspergillus; BioRad, Marnes-la-Coquette, France) allows for the detection Aspergillus galactomannan (GM) in serum. Relative to adults, however, a decreased sensitivity of the GM-ELISA in pediatric patients, particular in infants and non-neutropenic patient groups, has been reported.17 While cross-reactions with other fungal organisms are rare, false-positive results can be caused by contaminating GM in ß-lactam-antibiotics, dietary GM in pasta, cereals and formula milk, and cross reactivity with lipoteichoic acids of Biﬁdobacteria of the infantile gut microﬂora.14 Nevertheless, in a prospective cohort analysis in 56 children 0.6 to 18 years of age, using a cutoff value of 0.5, the GM-ELISA detected 66% of cases of proven/probable IA at a median of 10 days prior to the clinical or radiologic diagnosis with high speciﬁcity across all age groups. A very recent pediatric study also suggests utility of the GM-ELISA when applied to BAL ﬂuid of patients with suspected pulmonary aspergillosis.21 The beta-D glucan assay has been studied in adult patients with fungal infections.22 Due to the presence of (1,3)-ß-D-glucan in most opportunistic fungi, this test is not species-specific, but is sensitive for detection of invasive fungal pathogens; false-positive results may occur by several ways.14 Particularly in neonates, the assay is very promising for the diagnosis of IC. However, validation of the available assays in pediatric patients warrants further investigation.

Detection of Fungal DNA

Polymerase chain reaction (PCR) may be a powerful tool for early diagnosis of IFIs.23 No studies have addressed the issue in neonates; in children, PCR has not been specifically studied but is probably as good as in adults. Twice weekly screening in blood of high risk patients24 and specific detection of fungal pathogens in tissue specimens25 have emerged as the most feasible clinical applications to date.

CONCEPTS FOR MANAGEMENT AND PREVENTION

Invasive Candidiasis

Options for first-line therapy approved by the FDA and/or the EMEA for all pediatric age groups include liposomal amphotericin B (LAMB; 3 mg/kg QD), fluconazole (FCZ; 8–12 mg/kg QD), caspofungin (CAS; 50 mg/m² QD; day 1: 70 mg/m²; max.: 70 mg QD) and micafungin (MICA; <40 kg: 2 mg/kg QD; ≥40 kg: 100 mg QD).26-28

Criteria for selecting the initial treatment include the clinical status of the patient, organ impairment, concomitant medications, pretreatment with antifungal agents, the Candida species isolated and its resistance pattern: Patients who have received azole prophylaxis, are hemodynamically unstable or granulocytopenic, are colonized with C. glabrata or C. krusei, or are admitted at institutions with a high frequency of these organisms should receive a polyen or echinocandin upfront. As outcome depends critically on the prompt initiation of appropriate antifungal chemotherapy, risk-based, preemptive approaches have been proposed for adult ICU patients,28 however, no data exist for pediatric patients.11

Amphotericin B lipid complex (ABLC; 5 mg/kg QD; approval status) and voriconazole (VCZ; 4 mg/kg BID in children ≥13 years of age; interactions and adverse events) are options for second line therapy.30,31 Deoxycholate amphotericin B (DAMB) is still used in neonates and resistance-limited settings.

Similar to adults, central venous catheters should be removed promptly if feasible. Neutropenic patients should receive colony-stimulating factors (G-CSF or GM-CSF, respectively), and in patients on immunosuppressive therapy, steroids should be reduced, discontinued or replaced. The recommended duration of therapy for uncomplicated candidemia is 14 days after the clearance of the bloodstream and resolution of all symptoms. Following clearance of the bloodstream and clinical stabilization, oral consolidation with fluconazole is feasible for susceptible isolates. Fundoscopy is mandatory prior to end of treatment to rule out endophthalmitis.39

Treatment of other forms of IC (endocarditis, peritonitis, meningitis) is ill defined. It is based on pharmacological considerations such as a cidal mode of action and water-solubility and always includes the evaluation of surgical interventions; the additional use of flucytosine has a role in these situations.2,29

Invasive Aspergillosis

Antifungal therapy of IA frequently needs to be started pre-emptively on the basis of risk profiles, clinical, laboratory and imaging findings. However, all efforts
should be undertaken to obtain a microbiological diagnosis as the knowledge of the isolate is pivotal for treatment decisions.32

Options for first-line therapy approved by the FDA and/or the EMEA include VCZ (4 mg/kg BID ≥13 years; 7 mg BID <3 to 2 years) and liposomal amphotericin B (LAMB; 3 mg/kg QD; all age groups).2,3,13,34 Similar to the setting of IC, criteria for selecting one of these agents include organ impairment, concomitant medications, the type of preceding antifungal treatment, and the local epidemiology. In settings with a high frequency of zygomycosis, VCZ may not be a choice for pre-emptive therapy.32

Approved second-line options are ABLC (5 mg/kg QD) and CAS (50 mg/m² QD; day 1: 70 mg/m²; max.: 70 mg QD).30,35 While itraconazole and posaconazole are not approved in pediatric patients, DAMB may not be appropriate due to inferior outcomes in a randomized first-line trial.33 Based on solid preclinical and limited clinical data, VCZ currently is recommended for A. terreus infections and infections affecting the CNS.32

Dose escalation of LAMB to 10 mg/kg QD for the initial 14 days of treatment was not beneficial in a randomized comparative trial.34 Dose escalation of VCZ and CAS has not been studied and may be hazardous in the case of VCZ due to its nonlinear pharmacokinetics. Combination of standard doses of either VCZ or LAMB with CAS is promising, but valid clinical data are currently lacking.36 Therefore, combination therapy is only indicated in patients with clearly progressive or overwhelming disease.

Similar to adults, adjunctive surgical interventions need consideration in skin and soft tissue infections, sinus infections, impeding erosion of pulmonary arteries, and in operable CNS- and lung lesions. G-CSF or GM-CSF, respectively, is indicated in neutropenic patients, and reduction, discontinuation or replacement of steroids in immunosuppressed patients. The duration of therapy is individual and determined by the clinical and microbiological response. Clinical stabilization and at least a partial response provided, treatment can be consolidated with oral therapies.32

Emerging Fungal Pathogens

Amphotericin B is used as primary therapy for zygomycosis. Limited and uncontrolled data indicate an important role of both VCZ and PCZ in the management of Scedosporium and Fusarium infections.31,37,38 Notable exceptions are the zygomycetes that are not susceptible to VCZ; PCZ, in contrast, has shown encouraging clinical activity in the second line setting.25 Treatment of infections by the emerging fungal pathogens is an interdisciplinary challenge and needs to be individualized based on the patient’s organism and response to treatment.

Empirical Antifungal Therapy and Prophylaxis

Empirical antifungal therapy is an established standard of care in hemat-oncological patients with prolonged neutropenia (ANC <500/µl 10 days) and refractory or new fever that provides targeted prevention in a high-risk setting. Agents approved by the FDA and/or the EMEA for this indication in pediatric patients of all age groups include LAMB (1–3 mg/kg QD) and CAS (50 mg/m² QD; day 1: 70 mg/m²; max.: 70 mg QD).40,41

Prophylactic FCZ (8–12 mg/kg QD) remains a standard in antifungal prophylaxis post allogeneic hematopoietic stem cell transplantation (HSCT) due to its marked effect on long-term outcome. Alternatives may include the use of VCZ or micafungin (1 mg/kg QD).42,43 In patients with GVHD and increased immunosuppression, PCZ (200 mg TID) has been shown to prevent IFIs and IA.44 In adults with AML/MDS, PCZ (200 mg TID) had a significant impact on the frequency of IFIs and in particular, IA coupled with an overall survival benefit.45 Limited data in children >12 years of age suggest no differences in pharmacokinetics as compared to adults.46 Therefore, as a practical approach, PCZ may be given to children with high risk hematological malignancies or augmented immunosuppression for GVHD >12 years of age, and VCZ in younger children. Alternatives include the intermittent administration of LAMB (1 mg/kg QOD)47 or micafungin (1 mg/kg QD).42

Preventative Strategies in Preterm Neonates

Seventy-three percent of preterm infants with blood/CSF culture-proven infection either die or end up with neurodevelopmental sequelae even after prompt empiric treatment.48 Thus, severe late consequences of IFIs in preterm may only be avoided via preventative strategies.

Risk factors of IFI are difficult to eliminate as most of them are inherent to prematurity and intensive care, but cautious use of antibiotics, steroids, H2-blockers, enforced hygiene measures and promotion of maternal milk feeding are mandatory. Enhancing a bifidogenic enteric colonization is a promising option: in a randomized, controlled trial, Lactobacillus rhamnosus GG reduced enteric Candida colonisation by 90% in VLBW infants with no adverse events.49 Probiotics also modulate antibody- and cell-mediated immune responses to C. albicans and were shown to prevent NEC. The most compelling evidence thus far has been obtained with fluconazole. Five pre/post intervention, single-center studies have been published with a total of 919 preterm babies on fluconazole who developed 11 episodes of IFI (1.2%), compared to 908 not-treated infants with 68 IFIs (7.5%).49 Four randomized controlled trials, including a multicenter study,50–53 consistently report significant decreases of colonization and infection by Candida spp in the treated infants. Pooling the results, fluconazole reduced IFI risk by 75%, and all-cause mortality by 24% (OR 0.74; 95% CI. 0.58 – 0.95) in VLBW infants. Fluconazole is reported as safe, and did not lead to emergence of acquired resistance or to selection of species with intrinsic resistance. This was recently confirmed by two (8- and 10-year) analyses of sensitivities of fungal isolates in NICUs using fluconazole in preterm infants.54,55

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REFERENCES