An Update on the Diagnosis and Treatment of Invasive Mold Disease of the Central Nervous System in Children

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Epidemiological data of CNS IMD in pediatrics are limited. Aspergillus is the most frequently identified species, followed by other rare molds. Prompt diagnosis is of importance to define the optimal therapeutic management with respect to antifungal agent, dose, and evaluation of surgical intervention. The mortality rate of CNS IMD remains high. In this mini review we summarize the current knowledge on diagnosis and treatment of CNS IMD in pediatrics.

Key Words: aspergillosis, invasive mold disease, mucomycosis, pediatrics, rare mold infections,

Although epidemiological data on invasive mold disease (IMD) of the central nervous system (CNS IMD) in pediatrics are limited, the incidence seems to be increasing.[1,2] *Aspergillus i*s the most frequently identified species, followed by other rare molds.[1,2] Prompt diagnosis is of importance to define optimal therapeutic management.[1,3,4] Both morbidity and mortality rate of CNS IMD remains high.[1–3] Clinical symptoms are unspecific and may include a variety of focal and nonfocal neurological findings. However, about one-third of children with CNS IMD do not have symptoms.[5] Together with the high proportion of CNS involvement in pulmonary mold infections, the latter has prompted the recommendation of the most recent European Conference on Infections in Leukemia (ECIL) guidelines to consider cranial imaging in patients with pulmonary mold infection even if they are asymptomatic.[3]

The aim of this mini-review is to summarize the existing knowledge on the diagnosis and treatment of CNS IMD in pediatrics.

DIAGNOSTIC PILLARS FOR PEDIATRIC CNS IMD

Imaging

Due to limited radiation exposure and high sensitivity, magnetic resonance imaging (MRI) remains the preferable imaging tool in children with suspicion of CNS IMD, both for the initial diagnosis and for follow-up.[1] A limitation of the cranial MRI is the lack of fungal-specific findings and the difficulty in evaluating the results, especially in children with granulocytopenia or immunosuppression.[1,3] The most frequently reported findings in children with CNS IMD are fungal abscesses and inflammation of the parenchyma (cerebritis).[6] Data from a pediatric case series suggested that affection of cerebral blood vessels (infections and/or perivascular micro-bleeding) might indicate poor outcomes.[1,6]

Laboratory Evaluation: Microscopy and Culture

The gold standard for the definite diagnosis of CNS IMD involves cultures obtained by sterile procedure and/or histopathologic, cytopathologic or direct microscopic evaluation.[2,4] One of the main concerns is that cultures often lack sensitivity and may remain negative, therefore, negative culture results may not exclude CNS IMD. In most children with fungal CNS abscesses without the presence of fungal meningitis, culture and histology of the Cerebrospinal fluid (CSF) might not be indicative of CNS IMD, and therefore tissue biopsy of the CNS lesions is recommended.[1,2,4] However, brain tissue specimens are often difficult to obtain, especially in children with cancer and chemotherapy-associated thrombocytopenia and the potential risk of bleeding complications. Of importance, collection and storage specifications of samples are important, for example, to avoid the use of fixatives and to reassure the specimen's moisturizing.[1]

Non-culture Based Diagnostic Assays

Galactomannan (GM) assay is an adjunctive diagnostic tool, especially for the monitoring of children at risk for invasive aspergillosis (IA).[3,4] The recently published ECIL suggests that in children at high risk of

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TABLE 1. Pediatric Antifungal Agents and Dosage For CNS IMD

Antifungal Agent	Indication	Dose (age)
Liposomal amphotericin B	Invasive CNS aspergillosis	5 mg/kg per day in one dose (all ages)
	Invasive CNS mucormycosis	5–10 mg/kg per day in one dose (all ages)
Amphotericin B lipid complex	Invasive CNS aspergillosis	5mg/kg per day in one dose (children ≥1 month)
Voriconazole	Invasive CNS aspergillosis	Children aged 2–<12 years or 12–14 years and weighing <50 kg: 8 mg/kg (day 1, 9 mg/kg) twice daily intravenously or 9 mg/kg twice daily orally starting dose plus TDM Children aged ≥15 years or 12–14 years and weighing ≥50 kg:4 mg/kg (day 1, 6 mg/kg) twice daily intravenously or 200 mg twice daily orally starting dose plus TDM Children ≥2 years: Not approved; when used, starting doses as recommended for children aged 2–<12 years are recommended
Posaconazole	Invasive CNS mucormycosis	Intravenous solution≥2 years of age: 6 mg/kg once daily (max. 300mg; day 1: twice daily) Delayed released tablets >40kg: 300 mg once daily (day 1: twice daily) Oral suspension Not approved (EMA) 200 mg three times daily (FDA only for ≥ 13years) Powder for delayed-release oral suspension≤40kg: weight-based once-daily dosing (day 1: twice daily) For details, see SPC
Isavuconazole	Invasive CNS mucormycosis	10 mg/kg per day in one dose, the maximal dose of 372 mg isavuconazonium sulfate (d 1 and 2: three times daily) (Not approved for children)

CNS indicates central nervous system; EMA, European Medicines Agency; IMD, invasive mold disease; SPC, Summary of Product Characteristics; TDM, Therapeutic Drug Monitoring.

Invasive fungal disease who do not receive mold-active prophylaxis, prospective monitoring of serum GM two times per week is highly recommended for the prompt diagnosis of IA (A-II).[3,4] Data on GM assay validation in non-neutropenic pediatric patients and in CSF specimens are limited. Still, the ECIL guidelines recommend the GM evaluation in the CSF in immunocompromised patients with suspected CNS IMD, with a proposed threshold of 1.0.[3] Due to the low positive predictive values of the GM assay, negative results do not exclude the presence of CNS IMD in children, and, of importance, the assay does not detect a number of non-*Aspergillus* molds.[1,3]

The Beta D Glucan (BDG) assay detects BDG in the fungal wall, including *Aspergillus* spp., and was initially characterized as a useful adjunctive diagnostic tool in children with high clinical and radiological suspicion of Invasive fungal disease.[2] Currently, the optimal cutoff for the positivity of GM in CSF has not been defined. The main concern is that the present assay is associated with variable sensitivity and cross-reactivity with certain β-lactam antibiotics. A recently published meta-analysis including pediatric-specific evidence, indicates highly variable sensitivity, specificity, and positive and negative predictive values of the BDG assay.[7] Based on the above data, the ECIL pediatric guidelines recommend against the use of serum BDG in clinical decision-making (D-II).[3] Additionally, due to limited data on the evaluation of BDG in the CSF in children, no grading was suggested in the recommendations.[3]

Polymerase chain reaction (PCR) assay serum/plasma or bronchoalveolar lavage fluid was proposed as an adjunctive diagnostic tool for adults and children. Due to limited pediatric data on the validation and performance of the PCR in the prospective monitoring of CNS IMD, the current ECIL guidelines have not included molecular testing specific recommendations for children.[3] Initial evidence on the performance of PCR assays in detecting CNS IMD in adults was promising, as suggested by data derived from a small retrospective study using *Aspergillus*-specific nested PCR.[8] The sensitivity and specificity values were 1.0 (95% CI: 0.68–1) and 0.93 (95% CI: 0.77–0.98), respectively.[8] Similarly, a retrospective pediatric study tried to assess the diagnostic performance of both CNS GM and PCR testing in a small cohort of children (15 cases with and 32 cases without CNS IMD).[9] The results showed that GM and PCR in CSF or biopsies were useful for the diagnosis of CNS IMD in children with immunosuppression and for the final fungal species identification. The estimated sensitivity and specificity of CNS GM were 88% and 96% and of the CNS PCR assay 75% and 93%, respectively.[9]

TREATMENT PILLARS FOR PEDIATRIC CNS IMD

General Considerations

Prompt initiation of effective antifungal agents remains the cornerstone for the therapeutic management of CNS IMD.[1–3] For immunocompromised children, the control of predisposing factors, such as severe neutropenia or therapeutic doses of glucocorticosteroids, is highly recommended.[1,3,4] Evidence on the safety (toxicity) and efficacy of intrathecal or intraventricular antifungal administration in pediatrics are limited.[1] From the currently available antifungal agent classes, echinocandins have poor penetration through the blood-brain barrier due to their high molecular mass and their high protein binding, whereas antifungal triazoles and amphotericin B products have variable CNS disposition. New antifungal drugs, such as olorofim, might offer new treatment options in children with difficult-to-treat CNS IMD infections.[10] Duration of treatment is still to be defined and is determined by the resolution of clinical, laboratory, and radiographic findings.

Treatment of Pediatric CNS Aspergillosis

Voriconazole is the treatment of choice for CNS aspergillosis in children ≥2 years of age, and Therapeutic drug monitoring is highly recommended with serum levels >1–2 mg/L to ensure adequate concentrations in the CSF and CNS.[1,3,4] Amphotericin B is suggested for children intolerant or refractory to voriconazole.[1] Liposomal amphotericin B (5 mg/kg per day in one dose; max. 10 mg/kg and day) is suggested for all ages (Table 1)[3,4]; if not available, amphotericin B deoxycholate is the next best alternative (1.0–1.5 mg/kg and day for pharmacokinetic/pharmacodynamic reasons).[11] Flucytosine is not recommended for CNS aspergillosis due to a lack of evidence on clinical efficacy.[1] Evidence on combination antifungal therapy or posaconazole or isavuconazole to treat children with aggressive or refractory CNS aspergillosis is currently limited.

Treatment of Pediatric CNS Mucormycosis

High-dose liposomal amphotericin B (dose of 5–10 mg/kg) is the treatment of choice in children with CNS mucormycosis, while amphotericin B deoxycholate, due to limited CNS penetration and more frequent nephrotoxicity, or combination antifungal therapies including liposomal amphotericin B are alternative options with a lower recommendation grade.[3,12] Posaconazole has limited CNS penetration, though a novel powder for oral suspension with improved oral bioavailability and an IV formulation is now available

and approved.[13] Because experience with posaconazole is also limited, this drug can be used either in cases intolerant to amphotericin or as a step-down treatment.[10] Isavuconazole has shown good penetration in the CNS.[3,11] Clinical adult data of CNS IMD revealed increased clinical efficacy of isavuconazole, with an overall survival rate reaching almost 81%.[12,14] However, isavuconazole does not have a pediatric label to date. Prompt surgical debridement is an important pillar for the management of disseminated mucormycoses cases though the risk and benefits should be carefully assessed by a multidisciplinary expert group.[12] Data on the safety and efficacy of hyperbaric oxygen in children are limited.[3,10,15]

Treatment of Other CNS Rare Mold Infections

Pediatric data on the optimal treatment of CNS rare mold infections attributed to *Fusarium* spp. and *Scedosporium* spp. are lacking, and the current guidelines are mainly focused on extrapolating data from adult studies.[1,10,16] Due to the intrinsic high resistance of *Scedosporium s*pp. and of *Lomentospora prolificans* to antifungal agents, the currently available antifungal options are limited.[10,16] The combination of voriconazole with another class of antifungal drugs has revealed synergistic effects against both *Scedosporium* spp. and *L. prolificans*.[10,16] For fusariosis, treatment with voriconazole or liposomal amphotericin B is recommended.

CONCLUSIONS

The diagnosis relies on clinical suspicion and the current diagnostic tools need to be improved and validated in the pediatric setting. Prompt initiation of effective antifungal treatment, control of predisposing factors and extensive surgical intervention remain the cornerstone for optimal treatment. New antifungals might offer in the future additional treatment options in children.

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