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Cerebral Fungal Infection in Pediatric Cancer Patients

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Abstract Invasive fungal disease (IFD) significantly contributes to morbidity and mortality in pediatric cancer patients, especially in those with acute leukemia and allogeneic hematopoietic stem cell transplantation. Cerebral fungal infections are a particular severe form of IFD, as they are difficult to diagnose and require aggressive treatment, and cure rates are still unacceptably low. Here, we review the current data on epidemiology, diagnosis, and the management of cerebral fungal infection in pediatric cancer patients and outline important questions which have to be addressed by further research.

Keywords Invasive fungal infection · Central nervous system · Cancer · Child · Hematopoietic stem cell transplantation

Epidemiology of Cerebral Fungal Infection in Pediatric Oncology

While invasive fungal disease (IFD) is rarely observed in healthy children beyond the neonatal period, IFD represents a significant medical problem in children with cancer [1]. Among them, children with acute myeloblastic leukemia, recurrent acute leukemias, or allogeneic hematopoietic stem cell transplantation (HSCT) are at highest risk for IFD (estimates vary between 8 and 20 %) [2–12]. A moderate risk for IFD is observed in children with acute lymphoblastic leukemia, non-Hodgkin lymphoma, or autologous HSCT (risk approximately 3–8 %) [3–5, 7–12], whereas the risk of IFD is relatively low, but not neglectable, in children with Hodgkin lymphoma or solid tumors (risk approximately 1 %) [3, 4, 8–12]. The early diagnosis of IFD results in better outcome, but central nervous system (CNS) involvement is often difficult to diagnose and is extremely difficult to treat. Notably, treatment strategies in cerebral IFD may differ from invasive fungal infections of other organs, e.g., in regard to the choice and dosage of the antifungal compound and/or surgery. Unfortunately, despite the importance of cerebral fungal infections in pediatric cancer patients, data on their epidemiology and management in children are scarce.

Candida spp. and *Aspergillus* spp. are causing the vast majority of cerebral fungal infections in pediatric cancer patients. The reported incidence of invasive *Candida* infection in children with high-risk leukemia or after allogeneic HSCT varies between 3 and 15 % [2, 6, 13, 14]. Unfortunately, exact data on the cerebral manifestation of invasive *Candida* infections have not been systematically reported, and their occurrence appears to be underestimated in many centers [15, 16]. *Candida albicans* is the most frequently isolated pathogen in pediatric candidiasis, but other species such as *Candida parapsilosis*, *Candida glabrata*, *Candida tropicalis*, *Candida krusei*, *Candida dubliniensis*, *Candida lusitaniae*, and *Candida guilliermondi* are increasingly observed, which may have important implications regarding antifungal resistance (see details below) [2, 3, 17, 18]. Established risk factors for invasive *Candida* infections are prolonged neutropenia, treatment with corticosteroids, mucositis and other mucosal lesions, central venous lines and urinary catheters, parenteral nutrition, usage of broad-spectrum antibiotics, and severe graft-versus-host disease (GvHD) [3, 8, 14, 18–20].

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Yeasts other than *Candida* (e. g., *Trichosporon asahii*, *Geotrichum capitatum*, *Saccharomyces cerevisiae, Rhodotorula rubra*, *Hansenula anomala*, *Malassezia furfur*) rarely cause cerebral fungal infections in pediatric cancer patients, but the clinical outcome in infected patients is poor due to resistance issues [3, 21, 22]. Similarly, *Cryptococcus* species are not a common cause of cerebral fungal infection in pediatric cancer patients, which is in contrast to HIV patients. The epidemiology, clinical presentation, and treatment of cerebral cryptococcosis in this patient population have been reviewed elsewhere and are beyond the scope of this review [23].

Aspergillus species frequently cause IFD [24], and cerebral manifestations are observed in up to 20–40 % of children with invasive aspergillosis [9, 24–26]. Cerebral aspergillosis is associated with mortality rates of 50–100 % [9, 24–28]. *Aspergillus fumigatus* accounts for approximately 50 % of pediatric invasive aspergillosis cases, followed by infections with *Aspergillus flavus*, *Aspergillus nidulans*, *Aspergillus niger*, and *Aspergillus terreus* [17, 27]. In contrast to *Candida* spp., which are part of the commensal flora, *Aspergillus* spp. typically invade the organism via inhaling contaminated aerosols [28]. Hence, the primary manifestations of aspergillosis are usually infections of the lung or the sinuses, from which cerebral invasion may occur via the blood stream or local invasion [10, 26]. Risk factors for invasive aspergillosis include prolonged neutropenia, functional impairment of granulocytes and macrophages due to steroid therapy or HSCT, severe GvHD, and exposure to aerosols containing high concentrations of *Aspergillus,* for example, from compost, construction waste, or contaminated air filters [2, 14, 19, 24].

Other filamentous fungi which have been reported to cause cerebral fungal infections in pediatric cancer patients include *Fusarium* and *Scedosporium* species [5, 10]. Furthermore, dimorphic fungi such as *Histoplasma*, *Blastomyces*, or *Coccidioides* can cause cerebral infections in these patients, though their occurrence displays high geographical variation and is rather endemic [29–34]. Finally, *Zygomycetes* (e.g., *Rhizopus*, *Mucor*, *Rhizomucor*, *Absidia*) can be responsible for cerebral infections in pediatric cancer patients [17]. In this regard, a recent study has shown that acute lymphoblastic leukemia was by far the most frequent malignancy among 82 pediatric cancer patients with invasive infection due to *Zygomycetes* [17]. Among the patients included in this study, 24 % suffered from rhinocerebral manifestation, and mortality rates of children with rhinocerebral infection ranged from 40 to 67 % [17, 35, 36].

Clinical Presentation of Cerebral Fungal Infections in Pediatric Cancer Patients

The clinical presentation of cerebral fungal infections depends on the site of involvement and can be classified in a number of defined syndromes.

Cerebrovascular Events

Generally, fungi may invade the CNS *per continuitatem* (e.g., from infected sinuses) or via the blood stream from clinically silent or non-silent foci. Hence, the involvement of intracranial vascular structure is a hallmark of cerebral fungal infections, though vascular involvement itself may remain vague and rather constitutes the source of fungal meningitis and mass-occupying lesions, which are described below. Nevertheless, distinct cerebrovascular events such as stroke due to septic emboli, hemorrhagic lesions, or, occasionally, local irruption of brain arteries are the typical manifestations of cerebral fungal disease [27, 37]. The occurrence of such events should prompt the clinician to carefully evaluate pediatric cancer patients for the presence of IFD and to consider the initiation of empiric antifungal therapy. Fungal species which have been described to provoke cerebrovascular events in pediatric patients include species of *Aspergillus*, *Candida*, *Zygomycetes*, *Cryptococcus*, or *Coccidioides* [27, 38].

Cerebral Abscesses, Granulomas, and Other Space-Occupying Lesions

Cerebral fungal infections frequently present as single or multiple space-occupying lesions in terms of fungal abscesses, granulomas, or cystic lesions. Whereas the formation of one or more larger abscesses and granulomas is a hallmark of invasive aspergillosis [26, 27], multiple smaller abscesses, granulomas, or a mixture of both, is typical for cerebral *Candida* or *Cryptococcus* infections [39, 40]. In rare cases, cerebral fungal abscesses can be attributed to infection with *Blastomyces*, *Histoplasma*, *Coccidioides*, or *Zygomycetes* [29–34]. Frequent clinical signs of cerebral fungal abscesses are fever, focal neurological signs depending on localization, or abnormal mental status. However, it is important to note that neurological symptoms may occur late or may be missing in immunocompromised patients [27], and, on the other hand, may be due to other underlying complications, such as treatment-related toxicity.

Rhinocerebral Infections

Paranasal sinuses and nasal and otal cavities are common localizations of infections with *Zygomycetes* or *Aspergillus* spp., though sinusitis due to *Aspergillus* spp. appears to be less common in children compared to adults [10, 17, 41••]. From these cavities, fungi may invade into cranial bones (including the eye socket) and subsequently affect leptomeningeal and cerebral structures, in particular in the basi-frontal and basi-temporal region [38]. The typical symptoms of rhinocerebral fungal infections are headache, inflammation and protrusion of the eye, cranial nerve lesions, seizures, aphasia, and sheer tissue destruction [17, 37, 38]. Therefore, high suspicion is

needed in immunocompromised patients presenting with these symptoms, since rhinocerebral infections require prompt diagnosis and aggressive management [17].

Meningitis and Meningoencephalitis

Meningitis and meningoencephalitis are typical forms of cerebral infections with *Cryptococcus* spp., *Candida* spp., or of infections with *Blastomyces* spp., *Histoplasma* spp., or *Coccidioides* spp., although the latter are relatively rare [29–34, 42, 43]. Exclusive meningeal infection is a possible but very uncommon feature of cerebral infections with *Aspergillus* spp. or *Zygomycetes* [17, 26]. Although fungal meningitis can be associated with classical clinical signs such as headache, neck stiffness, photophobia, or cranial nerve abnormalities, the clinical presentation is often mild or unspecific, in particular in the immunocompromised host [39, 40, 42]. Hence, the early diagnosis of fungal meningitis requires a vigilant surveillance of patients at risk.

Diagnosis of Cerebral Invasive Fungal Infections

Diagnostic Imaging

Meningitis, meningoencephalitis, inflammatory granulomas, stroke due to vasculitis, and intracerebral and subarachnoid hemorrhage due to rupture of a mycotic aneurysm are possible complications of intracranial fungal infections. Therefore, magnetic resonance imaging (MRI) of the CNS is an important diagnostic tool to identify and monitor cerebral fungal infections in pediatric patients. Unfortunately, radiological signs can be subtle or even absent in the immunocompromised patient. In addition, abnormalities in diagnostic imaging are not specific for cerebral fungal infections, as bacterial and mycobacterial cerebral infections, the underlying malignancy and treatment-related toxicities may present with similar imaging features.

The role of routine sinus imaging such as by computerized tomography (CT) scans in otherwise asymptomatic patients with prolonged febrile neutropenia is uncertain, and data on the frequency of accompanying symptoms of sinonasal invasive fungal disease are scarce, in particular in immunocompromised children [44••]. Importantly, children younger than 2 years of age have not had sufficient pneumatization of the sinus cavities, and thus, sinus imaging is rarely informative in this age range. In addition, the potential consequences of radiation exposure by the use of CT scans or the need for general anesthesia which is often necessary in children in whom cerebral MRI is performed have to be considered. On the other hand, there is a clear indication of cerebral imaging, i.e., MRI in febrile neutropenic patients with otherwise unexplained neurological symptoms, and its results may help to guide further diagnostic procedures (such as biopsy) and therapeutic approaches (such as empiric therapy, surgery). If bone destruction is suspected on MRI, a CT scan should follow.

Intracerebral aspergillosis can cause complications such as aneurysm formation, hemorrhage, infarction, abscess formation, granulomas, meningitis, and cerebritis. The fungus can infiltrate the brain causing a breakdown of the parenchyma with hemorrhagic infarcts, septic infarcts, and focal cerebritis (Fig. 1a, g). The typical findings in MRI are multiple lesions in the cerebral hemispheres, basal ganglia, and corticomedullary junction; areas of petechial hemorrhage and paramagnetic substances; ring enhancement (in patients with less severe immunosuppression, Fig. 1i); grossly hemorrhagic lesions; and early vascular enhancement [45]. Aspergilloma show hypointense signal (Fig. 1a) on T1-weighted image (WI), mixed signal on T2WI (Fig. 1d–f). Low-signal intensity areas on T2*WI may be due to hemorrhage, free radicals produced by macrophages, or metal ion accumulation by the organism, although in immunosuppressed hosts, it usually represents areas of hemorrhage (Fig. 1b). Similar to bacterial abscesses, aspergillus abscesses may have rim enhancement (Fig. 1h, i) with central restricted diffusion (Fig. 1c) as a result of the increased cellularity of the fungal mass. According to a recent report, magnetic resonance spectroscopic (MRS) imaging of aspergilloma may show high levels of choline (Cho) and low levels of creatinine (Cr) and lactate with the absence of N-acetyl-aspartate (NAA) [46]. While multifocal infarctions are better seen in diffusion-weighted image (DWI) sequences, intraparenchymal hemorrhages are better evaluated on susceptibility-weighted images (SWI) sequences because of the susceptibility effects associated with deoxyhemoglobin, intracellular methemoglobin, and hemosiderin.

Zygomycetes are angioinvasive with hematogenous dissemination, vascular thrombosis, and necrosis, and often spread to the brain directly from the paranasal sinuses (Fig. 2). Therefore, CT is useful because it shows bone destruction, and the usual aspect is hyperdensity within the paranasal sinuses and bone destruction (Fig. 2a). MRI typically shows a hypointense structure on T2WI (Fig. 2b, c), but the signal can be of variable intensity. Due to angioinvasion, an infiltrative mass involving the sinuses and orbits or extending intracranial with meningeal involvement can often be seen. The vascular involvement of the cavernous sinus or large vessels with occlusions is a known complication with parenchymal abscesses and infarctions. Standard MRI includes DWI, which facilitates the diagnosis

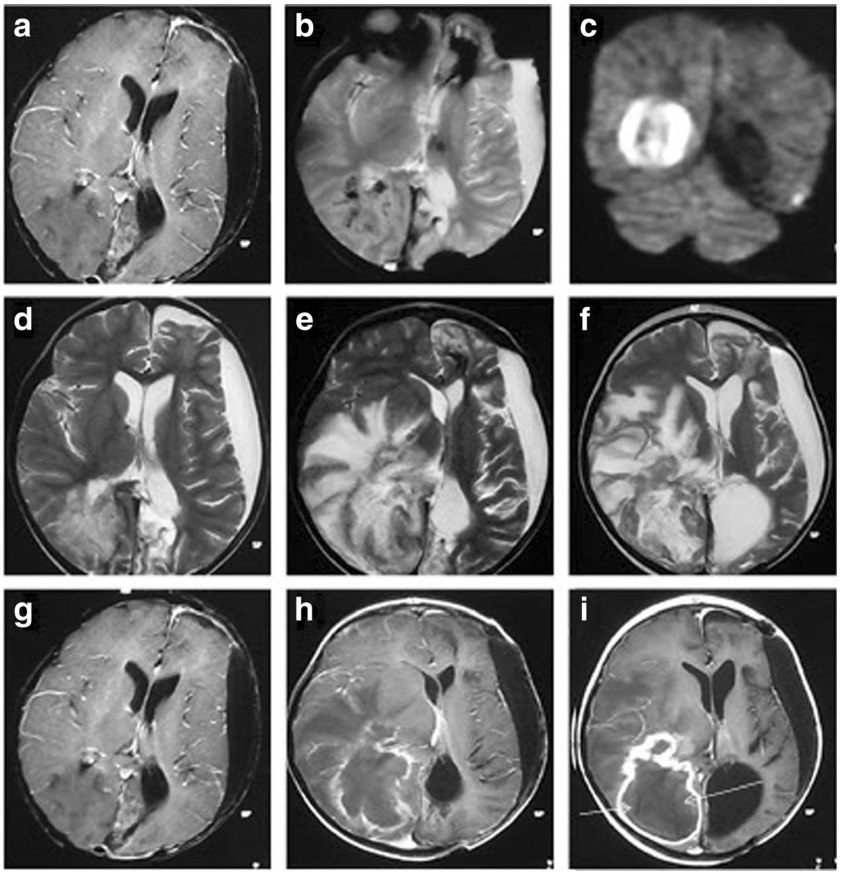

Fig. 1 A 7-year-old girl with relapsed acute lymphoblastic leukemia and cerebral aspergillosis. **a**–**c** *Aspergillus* granuloma. Axial T1-weighted image (WI) after contrast (**a**) shows a heterogeneous isointense cerebritis in the right parieto-occipital region. The lesion is partially hypointense on T2* (**b**). The low-signal intensity areas may be due to hemorrhage. Diffusion-weighted images (**c**) show a ring hyperintensity with central restricted diffusion and areas of hypointensity in the cavity. **d**–**f** T2WI in follow-up show a heterogeneous hyperintense lesion in the right parieto-occipital region (**d**). Axial T2WI (**e** and **f** after 30 and 60 days, respectively) show an ill-defined hypointense wall and increasing surrounding edema (**f**). **g**–**i** Post-contrast images show in the follow-up of 30 and 60 days intense enhancement of the mass lesion. In the first image (**g**), the lesion appears as an ill-defined isointense mass. The follow-up post-contrast axial T1WI (**h** and **i**) shows an abscess formation with peripheral enhancement. Note the typical non-enhancing intra-cavitatory projections (*arrows*). In addition, two more enhancing lesions are found in the thalamus (**i**)

of fungal cerebritis and cerebral abscess [47]. DWI can characterize fungal abscesses or acute infarcts secondary to vascular invasion and thrombosis by demonstrating restricted diffusion. A rare complication is a mycotic aneurysm formation with hemorrhage.

Cryptococcus typically spreads along the base of the skull and may involve the parenchyma, giving rise to cryptococcomas or may extend along the Virchow-Robin spaces to form "pseudocysts." MRI therefore shows dilated Virchow-Robin spaces and multiple enhancing parenchymal

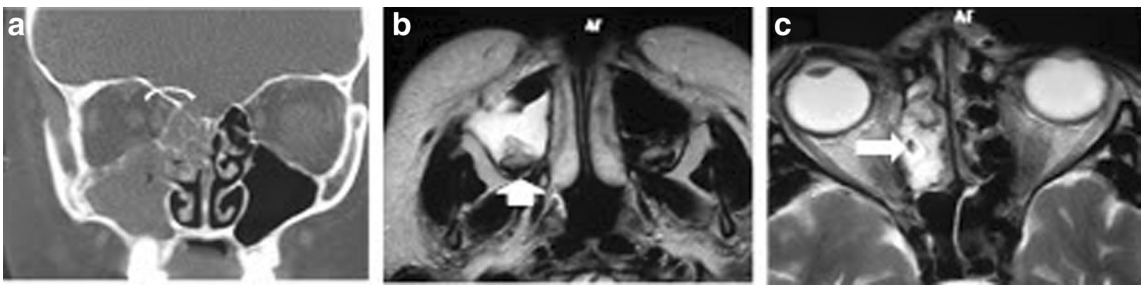

Fig. 2 A 10-year-old girl with aplastic anemia suffering from mucormycosis. **a** Computerized tomography shows the destruction of the frontobasis in the area of the cribriform plate (*curved arrow*). **b**, **c** Axial T2-weighted images (WI) show areas of hypointensity in the right maxillary and in the right ethmoidal sinus (*straight arrows*)

and leptomeningeal nodules, which may not enhance or may show rim.

Detection of Fungal Antigens

Galactomannan

Galactomannan (GM) is a polysaccharide cell wall component of all *Aspergillus* spp. which is released during cell growth [48]. Galactomannan can be detected by an FDA-approved enzyme immunoassay (Platelia, Bio-Rad, Hercules, CA, USA) [49••]. Based upon the results of multiple clinical trials, which were mainly performed in the adult population, GM positivity in serum, bronchoalveolar lavage (BAL), and cerebrospinal fluid (CSF) is included as a microbiological criterion in the revised definitions by the EORTC/MSG consensus group [50]. Although there are less data in pediatric patients, sensitivity and specificity of GM testing in children compares favorably to the adult data, and therefore, GM testing is also included in specific pediatric guidelines [49••]. It is important to note that causes for false-positivity of the GM test have to be considered, such as some batches of the β-lactam antibiotics piperacillin/tazobactam and ampicillin, cross-reactivity with fungal species other than *Aspergillus* spp. such as *Penicillium marneffei* or *Histoplasma capsulatum*, and cross-reactivity with transfused blood or antiglobulin sera and cyclophosphamide [41••]. On the other hand, systemic antifungal prophylaxis may decrease the performance of the test [51].

The majority of data on GM testing are derived from assessing the molecule in the serum, whereas considerably fewer studies on GM testing in BAL and CSF are available, in particular in the pediatric population [47, 51, 52]. For example, GM levels in the CSF in 5 adult patients with probable CNS aspergillosis were significantly higher than those of 16 control patients indicating the potential diagnostic value of GM in CSF. According to current pediatric guidelines, GM positivity in the CSF (cut-off 0.5) can support the diagnosis of central nervous system aspergillosis [48, 49••, 52, 53], although the test is not validated in this setting.

β-D-Glucan

β-D-glucan (BG) is a cell wall component of many pathogenic fungi such as *Aspergillus* and *Candida* spp., but can also be detected in invasive fungal infections due to *Fusarium*, *Trichosporon*, or *Saccharomyces*, but not in zygomycosis [54]. β-D-glucan may also be detected in a number of bacterial infections (e.g., *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*) and, importantly, even in healthy individuals. As GM, the EORTC/MSG consensus group included BG as mycological criterion in the revised definitions of invasive fungal disease. Most studies on BG testing use the Fungitell™ assay (Associates of Cap Cod, Inc Falmouth, MA, USA), which has been approved by the FDA [50]. In adults, various studies have shown that monitoring of BG in the serum may be a useful non-invasive method for early diagnosis of IFD [35]. A recent study in adults has determined BG concentrations in CSF of patients with probable or proven cerebral fungal infection (aspergillosis, histoplasmosis, and cryptococcal meningitis). These patients were all positively tested for BG (a cut-off value of 80 pg/mL was applied) with a mean concentration of 352 pg/mL. In contrast, 18 of 19 control samples were BG negative (mean concentration 32 pg/mL) [55].

Unfortunately, immunocompetent uninfected children have higher BG levels than adults [56], which were even in the positive range (defined for adults) in 15 % of uninfected children [49••]. Since the optimal cut-off for BG testing in children is unknown and remains to be defined, a positive test of serum BG may support the diagnosis of invasive fungal disease in children, and current pediatric guidelines recommend that all positive BG results have to be interpreted with caution. In addition, a number of factors causing false-positivity of BG have to be considered, such as *Candida* colonization, bacterial infections, and the use of some antibiotics such as cefepime, piperacillin/tazobactam, or meropenem [41••, 48].

Nucleic Acid Testing

There are limited data on the value of nucleic acid testing (e.g., by polymerase chain reaction, PCR) in fungal infections in children, with few studies including heterogeneous patient populations with different clinical conditions. In addition, most of these studies have also clear limitations due to technical and methodological problems. Whereas PCR-based assays have been shown to be a promising diagnostic approach to detect and to identify fungal pathogens rapidly and reliably both in blood and other clinical samples (such as BAL, CSF), most of these studies have been performed in adult patients [57–60]. For example, a recent study in adults has applied a PCR assay to detect *Aspergillus* DNA in CSF samples of patients with suspected CNS aspergillosis. In this study, PCR in CSF was positive in 8/8 samples with proven/probable, and in 4/22 samples of patients with possible CNS aspergillosis [61•]. Though potentially powerful, the detection of fungal DNA by PCR-based assays is complicated by low amounts of fungal DNA which can be isolated from infected tissues, blood, or CSF, in particular in small children [62]. Taken together, despite the fact that the performance of PCR-based techniques in children is unclear to date, these assays may be very helpful in individual cases of suspected cerebral fungal infection, but results need to be interpreted with caution and treatment decisions should certainly not be based solely on results of PCR assays.

Microscopy and Fungal Cultures

Generally, all tissue and CSF specimens of children with suspected invasive fungal infection should be subjected to microscopy for fungal structures, for culture, and, if possible, for further analysis including fungal DNA analysis (see above). The isolation of fungi and culture is considered as a gold standard for the definite diagnosis of IFD. Fungal culture also allows testing for antifungal resistance, which is extremely important not only in infections with rare fungal species but also because of the increasing incidence of azole resistance in *Aspergillus* spp. [63••]. In case of a negative culture, PCR-based techniques and immunohistochemistry may be helpful in specifying genus and species of a fungus, as it has been shown in a 10-year-old girl with rhinocerebral mucormycosis [64]. In addition, the genotyping of the fungus may reveal mutations in the fungal genome associated with reduced or susceptibility or even resistance to specific antifungal agents [65–67].

Extracerebral Manifestations of Invasive Fungal Infection

Since foci of cerebral fungal infections are often difficult to access and various investigations may reveal false-negative results, the diagnostic approach of extracerebral manifestations of invasive fungal disease may be helpful. For example, the imaging studies of the lung may show pulmonary infiltrates in a number of patients with cerebral aspergillosis, which may be easier to access by biopsy than cerebral infiltrates. Therefore, imaging studies of the lung and abdomen (liver, kidney, spleen) should be performed in patients with suspected cerebral fungal disease. At the same time, other causes of a cerebral infiltrate and/or neurologic abnormalities have to be considered, such as bacterial and viral infection, the underlying malignancy, or treatment-related toxicities. To this end, to prove or to exclude cerebral fungal infection may involve a number of investigations, and the usefulness of each investigation has to be determined on a case-to-case basis. Importantly, all possible investigations should be considered for each specimen obtained in order to increase the likelihood of a diagnosis, which, in turn, may have profound consequences on the therapeutic approach [68, 69].

Prevention of Cerebral Fungal Infection

There are no specific strategies to prevent cerebral fungal infection. However, since a significant number of cerebral infections is due to the dissemination of fungal infection primarily involving other organs (e.g., the lung), general recommendations of antifungal strategies might also result in a reduction of cerebral fungal infection.

The multiple approaches of non-pharmacologic anti-infective measures are applied in different centers [70]. Among these measures, HEPA-filtered rooms are an effective mean to reduce the risk of air-borne infections such as invasive pulmonary aspergillosis [71]. Whereas it is widely accepted that immunocompromised patients should avoid construction areas, the efficacy of other measures, such as restrictions of social contacts, pets, and food, is less clear. Although studies on the efficacy of these measures are warranted, they are almost impossible to perform due to the multitude and the heterogeneity of other confounding factors, such environment and other non-pharmacologic and pharmacologic measures [72•].

Recent pediatric guidelines recommend primary antifungal chemoprophylaxis for children at high risk for IFD (≥10 %), namely those with acute myeloid leukemia, recurrent acute leukemia, and after allogeneic HSCT during the time of neutropenia and during phases of pronounced immunosuppressive therapy for severe GvHD [49••]. Patients with acute lymphoblastic leukemia should receive systemic prophylaxis according to the presence of other risk factors, such as the use of high doses of corticosteroids [49••]. Depending on factors such as local epidemiology, patient's age, underlying disease, and co-medication, systemic antifungal prophylaxis may consist of a lipid formulation of amphotericin B (e.g., liposomal amphotericin B, amphotericin B lipid complex), an echinocandin (e.g., micafungin), or an azole (e.g., voriconazole, posaconazole, itraconazole, or fluconazole) [73]. Whereas most azoles can be administered either orally or intravenously, only intravenous formulations are available for amphotericin B and the echinocandins. It is important to note that the choice of antifungal prophylaxis in children is controversial, and different guideline groups have used different approaches regarding evidence synthesis and recommendation generation [49••, 74]. It is unclear whether antifungal compounds which can be found in a high concentration in the CSF (such as voriconazole) are more effective in preventing cerebral fungal disease than antifungal compounds which pass the blood-brain barrier not only to a small extent (such as posaconazole) [75–79].

Treatment of Cerebral Fungal Infection

Most of the evidence to treat cerebral fungal infection has been obtained in adults but may be transferred to children when considering the age specifics for antifungal compounds. If cerebral fungal infection is suspected, the choice of the antifungal drug should be restricted to agents which sufficiently pass the blood-brain-barrier, such as the lipid formulations of amphotericin B (e.g., amphotericin B lipid complex and liposomal amphotericin B) or the broad-spectrum triazole voriconazole. In contrast, the echinocandins do not seem to

achieve therapeutic levels in the CNS [80–82]. Amphotericin B and its lipid formulations are effective against the vast majority of fungi which can cause a cerebral infection in pediatric cancer patients, with the notable exception of *Aspergillus terreus*. Therefore, liposomal amphotericin B may be the first-line empiric antifungal therapy in patients with suspected cerebral fungal infection, in particular in life-threatening conditions and in children who had received azole-based antifungal prophylaxis [49••]. Similarly, voriconazole is highly effective against most fungi causing cerebral infections and, based on data in adults, is the recommended first-line therapy in patients with cerebral aspergillosis [49••, 82, 83]. However, it is important to note that voriconazole is not active against *Zygomycetes*, and an emerging resistance to voriconazole in *Aspergillus* spp. has been described [84, 85]. Although supported by a number of case reports [64], it is unclear to date whether combination antifungal therapy is more effective than monotherapy in treating cerebral fungal infection. Once a pathogen is identified, empirical antifungal therapy has to be adapted to the susceptibility of the fungus. It is currently unclear at what time point antifungal therapy in cerebral fungal infection can be discontinued, in particular in patients in whom cerebral MRI reveals residues of the infection.

In addition to the administration of antifungal agents, current pediatric guidelines recommend to improve host immunity, e.g. by tapering immunosuppressive therapy in allogeneic hematopoietic stem cell transplant recipients with GvHD, the use of colony stimulating factors such as G-CSF or granulocyte transfusions in the neutropenic host, although for the latter, a significant benefit has not been proven to date [49••]. The surgery of space-occupying fungal lesions, in particular of large abscesses or rhinocerebral manifestations of zygomycosis, has to be discussed in a multidisciplinary approach on a case-to-case basis. In this regard, a systematic literature analysis of 157 pediatric patients between 0 and 18 years of age suffering from zygomycosis has revealed that amphotericin B (often given in increased dosages) and surgery significantly improved outcome, but it remains unclear whether this finding is due of a selection bias [36].

Outlook

The occurrence of cerebral fungal infection in pediatric cancer patients is a severe medical condition, which is still associated with high morbidity and mortality. Despite the significance of this medical problem, there are very limited data on epidemiology, the value of diagnostic procedures, and therapeutic approaches in the pediatric population. Future research is particularly warranted to define optimal strategies for the early and reliable diagnosis of cerebral fungal infection in children, which may significantly differ from adults. Better diagnostics may also have an impact on therapeutic strategies, which are mainly derived from clinical studies in adults. An optimization of both diagnostics and treatment hopefully will lead to the better outcome of cerebral fungal infection in children undergoing therapy for cancer.

Compliance with Ethics Guidelines

Conflict of Interest Angela Haßler and Luciana Porto have no disclosures. Thomas Lehrnbecher served in the speaker's bureau of Astellas, Gilead Sciences, GlaxoSmithKline, Merck/MSD, and Pfizer; he also received a research grant from Gilead Sciences and is a consultant to Astellas, Gilead Sciences, and Merck/MSD.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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