Central Nervous System Fungal Infections in Children With Leukemia and Undergoing Hematopoietic Stem Cell Transplantation: A Retrospective Multicenter Study

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Background: Central nervous system fungal infections (CNSFI) are seen in patients with hematologic malignancies and have high morbidity and mortality. Because of their rarity, there is limited data on CNSFI in children with no established treatment protocols or guidelines.

Materials and Methods: In this multicenter retrospective study, 51 pediatric patients with leukemia, 6 of whom had undergone bone marrow transplantation, with proven or probable CNSFI were evaluated. Fungal infections were defined as proven or probable based on European Organisation for Research and Treatment of Cancer criteria. Proven CNSFI was diagnosed by appropriate central nervous system (CNS) imaging or tissue sample findings in combination with positive microbiological results of cerebrospinal fluid. A positive culture, microscopic evidence of hyphae, a positive result of the galactomannan assays are defined as positive microbiological evidence. Probable CNSFI was defined as appropriate CNS imaging findings together with proven or probable invasive fungal infections at another focus without CNS when there is no other explanatory condition. Data was collected by using the questionnaire form (Supplemental Digital Content 1, http://links.lww.com/JPHO/A541).

Results: Seventeen patients had proven, 34 patients had probable CNSFI. Headaches and seizures were the most common clinical findings. The median time between the onset of fever and diagnosis

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was 5 days. The most common fungal agent identified was *Aspergillus*. Sixteen patients received single-agent, 35 received combination antifungal therapy. Surgery was performed in 23 patients. Twenty-two patients (43%) died, 29 of the CNSFI episodes recovered with a 20% neurological sequelae.

Conclusion: CNSFIs should be considered in the differential diagnosis in patients with leukemia and refractory/recurrent fever, headache, neurologicalocular symptoms, and a radiologic-serological evaluation should be performed immediately. Early diagnosis and prompt management, both medical and surgical, are essential for improving clinical outcomes.

Key Words: central nervous system, fungal infections, leukemia, pediatrics

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Invasive fungal infections (IFI) may occur in immunocompromised patients receiving immunosuppressive therapy, such as hematologic malignancy, solid organ, and bone marrow transplantation (BMT), or primary immunodeficiency syndromes.[1] With the development of intensive treatment protocols in childhood cancers, treatment-related side effects are also increasing. Invasive fungal infections, and especially central nervous system fungal infections (CNSFI), are a significant cause of mortality and morbidity in patients with hematologic malignancies.[2] Because of its rarity, there is limited data on CNSFI in children with no established treatment protocols or guidelines. Mainly case reports and small case series were reported in the literature. The aim of this multicenter study was to evaluate the demographic, clinical, and laboratory characteristics, diagnostic and treatment methods, and survival rates of CNSFI in children with leukemia.

MATERIALS AND METHODS

A questionnaire (Supplementla Digital Content 1, http://links.lww.com/JPHO/A541) consisting of age, sex, diagnosis of primary disease and the stage at which the fungal infection developed, treatment protocol, use of central venous catheter, potential environmental risk factors, clinical findings, duration of fever, duration and severity of neutropenia, galactomannan (GM) in blood and cerebrospinal fluid (CSF), culture results (blood, urine, and cultures from lesions), time between the first day of febrile neutropenic episode and CNSFI diagnosis, cranial magnetic resonance imaging (MRI)/computerized tomography (CT) findings, the presence of concomitant IFI, prophylactic or empiric antifungal use, use of granulocyte suspensions, intensive care unit (ICU) support, surgical interventions, follow-up status, and neurological sequelae of patients was used to collect data retrospectively. Invasive fungal infections were diagnosed based on European Organisation for Research and Treatment of Cancer criteria.[3] Patients with proven or probable IFI and the ones with a positive diagnostic imaging and/or microbiological evidence of CNSFI were included in the study. Patients with leukemia with CNSFI were enrolled into the study from 23 pediatric hematology/oncology centers in Turkey, between 2005 and 2015.

RESULTS

Data of 51 patients (21 female, 30 male) diagnosed with leukemia and CNSFI from 23 centers were evaluated. The demographic characteristics of patients and the underlying hematologic diseases are shown in Table 1. Six patients had undergone BMT. The median age was 7 years (20 mo to 18 y). The characteristics of CNSFI episodes are shown in Table 2. It has been demonstrated that there was a concomitant construction in the hospitals in 16 episodes (32%). The most frequent neurological findings were seizure, headache, ophthalmologic problems, cranial nerve involvement, and tremor. Sex, age, and the final status of the patients included in the study were evaluated, mortality was 42% in females and 45% in males, with no statistically significant difference ($P > 0.05$).

Diagnostic tests and results are shown in Table 3. Blood and urine cultures were obtained from all of the cases. In 5 cases microbiological evidence of fungi was observed in blood cultures. These were *Candida albicans* in 4, *Candida krusei* in 1. In 10 patients CSF cultures were obtained, *Geotrichum capitatum* was observed in one case and *C. albicans* in another case. Cultures from blood or CSF were never positive in patients with mold infections. In 17 patients tissue specimen from the brain lesions/abscess was obtained surgically for pathology and microbiological evaluation. In 14 of these cases, microbiological evidence of fungi was observed: *Aspergillus* spp. in 7, *Candida* spp. in 2, *mucormycosis* in 2, and other fungi in 3 (Table 3).

According to European Organisation for Research and Treatment of Cancer criteria,[3] 17 patients (33%) had proven, and 34 patients (67%) had probable CNSFI. In a patient in whom there was IFI of the lung, bronchoalveolar lavage specimen revealed *C. krusei*. In 6 additional patients, pathology reported the presence of hyphae (Table 3). GM was found to be positive at least twice in serum in 27 patients, and in CSF in 2 patients.

MRI was performed in all of the patients and the imaging findings are shown in Table 3. In the MRI, 20 patients had a single lesion, whereas 31 had multiple lesions in the brain parenchyma. The lesions were in the form of brain abscess in 18 patients. In all patients, thorax CT and abdominal ultrasound were performed. Twenty-eight (56%) patients had radiologic evidence of IFI in additional sites other than the brain (lung involvement in 28, hepatosplenic involvement in 5, paranasal in 9, and renal involvement in 1 patient) (Table 2).

All patients were receiving broad-spectrum antibiotics because of febrile neutropenia and some were receiving empiric antifungals because of prolonged neutropenic fever when they were diagnosed with CNSFI. Treatment modalities and results are summarized in Table 4. Sixteen patients (32%) received a single antifungal agent (voriconazole, liposomal amphotericin). Thirty-five of the patients (68%) were treated with the combination of antifungal agents (liposomal amphotericin, voriconazole, caspofungin, and posaconazole). Surgery was performed in 23 patients. Forty-one patients had central venous catheters. Granulocyte suspension was used in 8 patients, 28 patients were monitored in the ICU and extracorporeal membrane oxygenation was used in 1 patient. All these patients needed ICU follow-up because of CNSFI. In this study, 22 patients (43%) died. Twelve of these 22 patients were in remission and 10 were not in remission. Three of 10 who were not in remission had refractory disease. The other 7 patients were newly diagnosed leukemia patients receiving induction therapy. All patients died while diagnosed with CNSFI. Seven of the 22 patients who died had undergone surgical procedures. The survival of the patients according to surgery and disease is shown in Table 4.

In 2 patients with central nervous system (CNS) involvement at the time of diagnosis, 1 recovered with

sequelae and 1 died. There were no statistically significant numbers of patients to compare. In patients diagnosed with invasive fungal infection, blood GM positivity did not have a significant effect related to the end state ($P > 0.05$). No significant difference was found between taking antifungal prophylaxis before diagnosis of the disease on mortality and sequelae ($P > 0.05$). There was no significant difference in mortality and sequelae between those who underwent surgery and those who did not ($P > 0.05$). Also, there was no significant difference in time to count recovery from diagnosis of CNSFI in those who had surgery versus who did not ($P > 0.05$). The effect of combined antifungal therapy on mortality could not be demonstrated. However, a significant relationship was found between the remission status of the primary disease at the time of diagnosis and mortality ($P < 0.05$). Significantly higher mortality was found in patients who were not in remission with primary disease (Table 5).

DISCUSSION

Despite advances in diagnosis and treatment, IFIs are a significant cause of morbidity and mortality, especially in patients with hematologic malignancies.[4,5] The incidence of IFI in patients with hematologic malignancies is reported to be between 3.5% and 23.4% in different studies.[5–8] The mortality is reported to be as high as 21% to 48%.[5,9,10] CNSFI are rare and even in multicenter studies, the number of patients is not high. Its frequency among all IFIs has been reported as 1.4%.[11] One of the largest series of fungal infections in the literature has 89 cases enrolled, of which only 23 cases were pediatric (26%).[12] Studies enrolling only children have a very limited number of patients. Dotis et al[13] reported the results of 90 children with CNS aspergillosis, of whom 45% had leukemia. The present study differs from the literature by having the largest number of children with leukemia and CNSFI. The number of reported CNSFI cases at each center in this study in 10 years is a maximum of 9 per center. In a study which enrolled both adult and pediatric patients from 34 centers, the number of patients per center was reported to be <1.[12]

In this study, CNSFI is more common in males as reported in the literature. Although it might be because of a higher rate of childhood leukemia in males.[14] Risk factors for IFI include the type of underlying malignancy, remission status, duration and severity of neutropenia, and use of central venous catheters. Patients with acute myeloid leukemia are more prone to fungal infections. However, as more than 80% of all leukemias detected in childhood are acute lymphoblastic leukemia (ALL), and CNSFI occurs mostly in ALL cases as in our study[15] and mostly during induction treatment.[16] Candoni et al[12] reported that CNSFI was more common in patients with ALL and in relapsed/refractory patients, 74% of the patients were neutropenic. In our study, most episodes (66%) occurred during the early intensification phase of the BFM ALL protocol. Neutrophil counts were <500/mm^3 in 96% of neutropenic episodes, most patients had severe and prolonged neutropenia, and 13/51 of the patients were not in remission. Environmental factors and cultural habits may contribute to the development of fungal infection.[17] In particular, construction works in hospitals produce airborne fungal spores and considerably increase the risk of exposure of hemato-oncologic patients.[18] In our cohort, construction work was reported in 16 cases, and incense use was reported in 1 case.

TABLE 1. Characteristics of Patients

Patients	N (%)
Number	
Age (y)	51 (100)
Median (range)	7 (20 mo-18 y)
<2	2
>2	49
Sex	
Female	21 (41)
Male	30 (59)
Primary disease	
Acute lymphoblastic leukemia	42 (82.3)
First diagnosis	30
Relapsed/refractory	12
Acute myeloblastic leukemia	3 (5.8)
Other (bone marrow transplant patients)	6 (11.7)
Thalassemia major	1
Chronic myeloid leukemia	1
Aplastic anemia	2
Acute lymphoblastic leukemia	2

The most common clinical finding of IFI is fever. Invasive fungal infections should be considered in neutropenic cases with persistent fever despite antibiotics. The early signs of CNSFI may be very subtle, which delays the

TABLE 2. Characteristics of IFI Episodes

Characteristics	Patient (n = 51), N (%)
Risk factors	
Use of catheter	41 (82)
Construction work	16 (32)
Use of incense	1 (2)
Use of prophylactic antifungal drug	16 (31)
Fluconazole	14
Itraconazole	1
Posaconazole	1
Neutrophil count	
Median (range)	80 (0-1550)/mm^3
<100/mm^3	27 episodes
Duration of neutropenia	
Median (range)	13 (3-35)/day
>10 days	30
Duration of fever	15 (1-60)/day
Median (range)	9
>10 days	11
Time between fever and diagnosis	
Median (range)/day	5 (6 h-22 d)
Clinical findings	
Neurological findings	
Seizure	32 (62)
Headache	25 (49)
Optical problems	14 (27)
Tremor	5 (10)
Cranial nerve involvement	5 (10)
Other	
Fever	51 (100)
Nasal congestion	9 (18)
Skin/nail lesions	8 (16)
Miyalgia	5 (10)
Concomitant IFI of other sites	
Lung involvement	28
Paranasal	9 (18)
Hepatosplenic involvement	5 (10)
Renal	1 (2)

IFI indicates invasive fungal infection.

TABLE 3. Diagnostic Procedures

	Positive Result/Done (%)
Positive culture	22/51 (43.1)
Brain tissue	14/17 (82.3)
Aspergillus spp.	7 (50)
A. flavus	4 (28.5)
A. niger	1 (7.1)
A. fumigatus	1 (7.1)
Other	1 (7.1)
Candida spp.	2 (14.2)
C. albicans	2
Mucor	2 (14.2)
Others	3 (21.4)
Saprocheata clavirata	1
Tricoderma longibrachitum	1
Tricoderma harzianum	1
Blood	5/51 (10)
C. krusei	1
C. albicans	4
CSF	2/10 (20)
Geotrichum capitatum	1
C. *albicans*	1
Bronchi	1/3 (33)
C. krusei	1
Hyphae	6
CSF	2
Broncoalveolar lavage	2
Brain tissue	2
Galactomannan antigen positivity	29/39 (74.3)
In serum	27/37 (72.9)
In CSF	2/2
CSF findings	8/10 (80)
Increased protein	9/10
Increased cell (PNL)	3/10
Imaging (MRI/CT)	
Number of lesions	
Single lesion	20 (39.2)
More than one lesion	31 (60.8)
Location of lesions	
Leptomeningeal enhancement	7 (13.7)
Ekstraaxial (sinonasal, skull base)	9 (17.6))
Parenchymal lesion	51 (100)
Brain abscess	18 (35.2)
Others (granuloma, infarct and cerebritis)	8 (15.6)
Vascular involvement	3 (5.8)

CSF indicates cerebrospinal fluid; CT, computed tomography; MRI, magnetic resonance imaging; PNL, polymorphonuclear leukocyte.

TABLE 4. Treatment Characteristics of the Patients and Outcome

Type of Therapy	Patients (n = 51), N (%)
Monotherapy	16 (32)
Voriconazole	3
AmB	13
Combined therapy	35 (68)
AmB+ vori	22
AmB+ caspo	4
Amp B+posa	4
Vori+caspo	1
> 2 antifungal agents*	4
Surgery†	23 (45)
Surviving with sequale	10 (20)
Without sequale	19 (38)
Exitus	22 (43)

AmB indicates liposomal amphotericine B; vori, voriconazole; caspo, caspofungin; posa, posaconasol.
*Including micafungin, anidulafungin and 5 flucytosine.
†Extraventricular drainage in 2 patients.

diagnosis. In our patients, the most frequent neurological findings were seizure, headache, ophthalmologic problems, personality changes, fine tremors in the hands, nasal congestion, and myalgia. The presence of CNS-specific neurological symptoms such as convulsions and headaches are often indicative of advanced disease.[19] In our series, 21 of 32 patients with reported seizures have died. A neurological examination should be done daily in all patients with malignancy and fever.

Although advances in laboratory and radiology techniques have led to more efficient and earlier recognition of fungal infections recently, diagnosis is still difficult. Serum GM level is a supporting finding in the early diagnosis of invasive aspergillus infections. The sensitivity and specificity are reported as 82% (73% to 90%) and 81% (72% to 90%), respectively.[20] Serum GM levels could be evaluated in 37 patients and were found positive in 27. In 14 of these patients, the fungal agents were also isolated in surgical tissue samples. The role and standard range of GM in non-blood samples are still controversial. Although the role of a positive CSF GM test in diagnosis is limited, it may help in the early diagnosis and therapy.[21] However, the clinical state of patients with CNSFI is not always stable for a lumbar puncture. In our series, only 2 patients were evaluated for GM in the CSF and both were found to be positive.

Cranial CT/MRI is the most important imaging modality in the diagnosis of CNSFI. Imaging findings may be categorized as parenchymal (abscess, granulomas, cerebritis), vascular (vasculitis), and extra-axial (meningitis).[22,23] Necrotizing angiitis, thrombosis, and infarcts may develop because of fungal obstruction of the medium-large vessels.[24] Hemorrhagic infarcts can also cause septic infarction and cerebritis-abscesses.[23] In our study, a radiologic examination was performed in all patients. All had an MRI, some with an additional CT scan. Parenchymal involvement was the most common finding. Only some series in the literature have reported detailed radiologic findings. In the limited series in the literature that have reported radiologic findings, most reported parenchymal abscess.[13,19,25–29] In this study, 18 patients (of which 12 had aspergillus) had a radiologically visualized abscess.

In patients with IFI, the infectious agent usually reaches the brain hematogenously.[30] *Candida*, cryptococcoses, and especially *Aspergillus* are the most common agents affecting the CNS.[22] However, less common fungi should also be considered in the differential diagnosis. Some fungi are considered endemic in some geographical regions.[17] Aspergillus was the most frequently isolated agent in our series followed by *Candida* spp. However, rare fungal agents such as mucormycosis, *Saprocheata clavirata*, *Tricoderma longibrachitum*, and *Harzianum* were also detected in our series. CNSFI may be accompanied by the involvement of other organs, most commonly the lungs, followed by paranasal sinuses (PSs) and skin.[4,15,16] CNSFI was most commonly accompanied by lung involvement, followed by paranasal IFI in our patients. In our recently published study, in 40 children with leukemia and hepatosplenic fungal infection, 57% were accompanied by fungal infection in other regions, most commonly the lungs.[31]

TABLE 5. Relationship of Surgery and Disease Remission With the End State

	Exitus, N (%)	With Sequel, N (%)	Without Sequel, N (%)	Total, N (%)
Primary disease status				
Remission	12 (31.5)	9 (24)	17 (44.5)	38 (100)
Nonremission	10 (76.9)	1 (7.7)	2 (15.4)	13 (100)
Surgery				
Yes	7 (30)	7 (30)	9 (40)	23 (100)
No	15 (53)	3 (11)	10 (36)	28 (100)

Thirty-one percent of our patients who developed CNSFI were receiving antifungal prophylaxis. We could not find any data in the literature on whether antifungal prophylaxis used in patients with high-risk hematologic malignancy or BMT prevented especially CNSFI.

The current antifungal agents for IFI contain polyenes such as amphotericin B (AmB), liposomal amphotericin B (L AmB), flucytosine, triazoles such as fluconazole, itraconazole, voriconazole, posaconazole, and isavuconazole; and echinocandins like caspofungin, micafungin, and anidulafungin.[32] Amphotericin B has been used in the treatment of IFI since 1956, and new antifungals have been in use for the last 20 years.[33] Despite these new antifungal drugs, mortality is still high. Mortality rates in case series are higher compared with case reports (71% vs. 38%).[13] Invasive fungal infections of the CNS are difficult to treat especially in immunocompromised patients. The distribution of antifungal drugs in CSF varies.[34] Amphotericin B, the echinocandins, itraconazole, and posaconazole have limited CNS penetration. Fluconazole and 5-fluorocytosine penetrate well into the CNS but have a narrow spectrum. Voriconazole is well distributed in the CSF and is reported as the first-line therapy for especially CNS aspergillosis.[35] However, AmB/L AmB is the first-line agent for the treatment of mucormycosis.[27,36]

In high-risk patients, IFI should be considered in cases of persistent fever, and empirical antifungal therapy should be initiated. Modifications are made according to laboratory findings or the focus of infection. Empirical antifungal treatment was initiated in all of our patients, most commonly L AmB. At the time of CNSFI diagnosis, 72% of our patients were receiving empirical antifungal treatment. Voriconazole was added if the patient deteriorated clinical findings indicated aspergillus. When Candida infection was considered, echinocandins were added. Combination or sequential treatments have been reported in series in the literature.[37] As there are no randomized studies, there is no evidence to support combination antifungal therapy in CNSFI, however, most of these patients are clinically in very poor conditions and have a high risk of mortality and have been treated by combination antifungal agents. In our series, 69% were treated by combination antifungal agents. Although local (intralesional, intrathecal) antifungal therapy is rarely used in CNSFI, its efficacy is questionable. In the literature, there are cases where Amb B is administered intrathecally with systemic treatment and reported to contribute to outcome.[38,39] However, it has been reported that this should only be applied to selected cases because it is not included in the guidelines and may cause morbidity. In our series, 2 patients received intrathecal Amp B in addition to systemic treatment, however, both patients died because the infection could not be controlled.

Information on the optimal duration of antifungal therapy is inconclusive. It has been recommended that antifungal treatment should continue as long as immunosuppressive therapy continues in patients with documented IFI.[40] Antifungal treatment was continued in our patients during the immunosuppressive treatment. The median duration of antifungal treatment was 159 days (range: 30 to 730).

The role of granulocyte transfusions in IFI is unclear. A review concluded that there is insufficient evidence to determine whether it affects mortality.[41] In our series, 8 patients received granulocyte transfusion, 5 of whom died. It has been stated in the literature that IFI increase the need for intensive care in immunosuppressive patients.[42] In our series, 25 patients (48%) needed intensive care. Twelve of these patients died despite all supportive treatment, 3 of whom had refractory/progressive leukemia.

Surgical debridement of infected tissue in the PS or brain abscesses is recommended.[43] Approximately 10% of CNSFI may require surgical intervention. Because of the location of the lesion, surgery may not always be possible.[16] In fungal lesions of the PS, surgical intervention has been reported in about 30% of the cases.[12,13] In our study, surgical intervention for the CNS lesion was done in 45% of the cases. Surgical intervention has been reported to cause a 2-fold reduction in mortality, especially in aspergillus cases. Four cases required more than 1^{2-4} surgical procedure. Complications such as bleeding and infections may occur after surgery. In our series, 7 patients (30.4%), who underwent surgery died because of the progression of the primary disease. There were no deaths because of complications of surgery.

CNSFI has a poor prognosis with ~70% mortality,[13] surgical treatment has been reported as an important prognostic factor.[13] We believe the surgical interventions in this study contributed to the success of the treatment. In our study, 22 patients (43%) died; 57% of the CNSFI episodes recovered, 10 patients (19.6%) with neurological sequelae. Our study contains the largest number of children with hematologic malignancies and CNSFI in the literature. All of the patients with neurological sequelae had convulsions during the diagnosis of CNSFI except for 1 patient, and status epilepticus was observed in 1 patient. There was no cerebral bleeding in patients with neurological sequelae. Only 6 of them had surgery. In patients without neurological sequelae, at least 1 neurological symptom was observed during the diagnosis of CNS IFI. Lauten et al [44] reported that 46% of 29 pediatric patients developed severe neurological sequelae. This rate is quite high compared with our study, although the diagnosis of the disease is similar. The majority of the patients had leukemia and the number of adolescents was significantly higher. We think that the low rate in our study may be because of our lower number of adolescent patients ($n = 20$).

Potential limitations of the study include the following: since there is no data on the incidence of leukemia in each center, the frequency of CNSFI could not be determined for the whole group. In this study, 9 of the 51 cases with CNSFI, were diagnosed and treated at one center (Istanbul University-Cerrahpasa [IUC]); over the study period, in the IUC, of 207 children with leukemia, there were 350 episodes with febrile neutropenia, 109 episodes were with prolonged neutropenia and fever (> 7 d), all of whom had imaging

done and in 9/109 (9%) there were radiologic findings suggestive of CNSFI. Environmental factors in this multicentric study were not similar in all centers based on the retrospective evaluation of the cases. As stated in the results section some centers had a lot of construction which is reported to be a risk factor for fungal infections.[45] In some centers serum GM testing could not be done routinely. We cannot conclude whether monotherapy or combination antifungal treatment should be used in CNSFI. However, the spectrum of fungal agents detected in our study, including rare species suggest that antifungals with a large spectrum and a high penetration to the CNS should be recommended. Also, there were no standard surgery procedures because of the multicentric approach.

In conclusion, CNSFI is rare, and causes high mortality and morbidity. Early diagnosis and prompt treatment, both medical and surgical, are essential to improve clinical outcomes. The physician should be vigilant about ambiguous complaints and signs in the physical examination. In case of persistent or recurring fever with ambiguous symptoms such as headache, neurologicalocular findings, CNSFI should be considered in the differential diagnosis, and radiologic-serologic evaluation should be promptly performed. The most important observation from this study is patients with CNSFI can present with seizures, headache, and visual symptoms which need prompt evaluation.

REFERENCES

1. Fisher BT, Robinson PD, Lehrnbecher T, et al. Risk factors for invasive fungal disease in pediatric cancer and hematopoietic stem cell transplantation: a systematic review. *J Pediatric Infect Dis Soc*. 2018;7:191–198.
2. Ruhnke M, Behre G, Buchheidt D, et al. Diagnosis of invasive fungal diseases in haematology and oncology: 2018 update of the recommendations of the infectious diseases working party of the German society for hematology and medical oncology (AGIHO). *Mycoses*. 2018;61:796–813.
3. Donnelly JP, Chen SC, Kauffman CA, et al. Revision and update of the Consensus Definitions of Invasive Fungal Disease From the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. *Clin Infect Dis*. 2020;71:1367–1376.
4. Ruijters VJ, Oosterom N, Wolfs TFW, et al. Frequency and determinants of invasive fungal infections in children with solid and hematologic malignancies in a nonallogeneic stem cell transplantation setting: a narrative review. *J Pediatr Hematol Oncol*. 2019;41:345–354.
5. Mor M, Gilad G, Kornreich L, et al. Invasive fungal infections in pediatric oncology. *Pediatr Blood Cancer*. 2011;56:1092–1097.
6. Sano H, Kobayashi R, Suzuki D, et al. Bacteremia during neutropenia is a predictive factor for invasive fungal infection in children. *Pediatr Int*. 2013;55:145–150.
7. Avcu G, Karapinar DY, Akinci AB, et al. Utility of the serum galactomannan assay for the diagnosis of invasive aspergillosis in children with acute lymphoblastic leukemia. *Int J Infect Dis*. 2017;54:8–12.
8. Agarwal V, Joyce M. Microbiologically documented fungal infections in pediatric patients with acute myeloid leukemia: 12.5-year experience at a single institution. *J Pediatr Hematol Oncol*. 2014;36:e528–e532.
9. Castagnola E, Cesaro S, Giacchino M, et al. Fungal infections in children with cancer: a prospective, multicenter surveillance study. *Pediatr Infect Dis J*. 2006;25:634–639.
10. Kobayashi R, Kaneda M, Sato T, et al. The clinical feature of invasive fungal infection in pediatric patients with hematologic and malignant diseases: a 10-year analysis at a single institution at Japan. *J Pediatr Hematol Oncol*. 2008;30:886–890.
11. Lehrnbecher T, Frank C, Engels K, et al. Trends in the postmortem epidemiology of invasive fungal infections at a university hospital. *J Infect*. 2010;61:259–265.
12. Candoni A, Klimko N, Busca A, et al. Fungal infections of the central nervous system and paranasal sinuses in onco-haematologic patients. Epidemiological study reporting the diagnostic-therapeutic approach and outcome in 89 cases. *Mycoses*. 2019; 62:252–260.
13. Dotis J, Iosifidis E, Roilides E. Central nervous system aspergillosis in children: a systematic review of reported cases. *Int J Infect Dis*. 2007;11:381–393.
14. Sethi PK, Khanna L, Batra A, et al. Central nervous system fungal infections: observations from a large tertiary hospital in northern India. *Clin Neurol Neurosurg*. 2012;114:1232–1237.
15. Lashkari HP, Fernandes N, Alva K, et al. Central nervous system fungal infection and acute lymphoblastic leukemia in children: what is the optimal duration of antifungal therapy? *J Pediatr Hematol Oncol*. 2017;39:e312–e317.
16. Ramanathan S, Kate S, Kembhavi S, et al. A retrospective analysis of invasive fungal diseases (IFD) of the central nervous system in children with lymphoid malignancies. *J Pediatr Hematol Oncol*. 2019;42:e202–e206
17. Schwartz S, Kontoyiannis DP, Harrison T, et al. Advances in the diagnosis and treatment of fungal infections of the CNS. *Lancet Neurol*. 2018;17:362–372.
18. Kanamori H, Rutala WA, Sickbert-Bennett EE, et al. Review of fungal outbreaks and infection prevention in healthcare settings during construction and renovation. *Clin Infect Dis*. 2015;61:433–444.
19. Economides MP, Ballester LY, Kumar VA, et al. Invasive mold infections of the central nervous system in patients with hematologic cancer or stem cell transplantation (2000–2016): uncommon, with improved survival but still deadly often. *J Infect*. 2017;75:572–580.
20. Leeflang MM, Debets-Ossenkopp YJ, Wang J, et al. Galactomannan detection for invasive aspergillosis in immunocompromised patients. *Cochrane Database Syst Rev*. 2015;12:Cd007394.
21. Lehrnbecher T, Rath PM, Attarbaschi A, et al. Galactomannan and PCR in the central nervous system to detect invasive mold disease—a retrospective analysis in immunocompromised children. *Sci Rep*. 2019;9:12950.
22. Mathur M, Johnson CE, Sze G. Fungal infections of the central nervous system. *Neuroimaging Clin N Am*. 2012;22:609–632.
23. Caceres A, Avila ML, Herrera ML. Fungal infections in pediatric neurosurgery. *Childs Nerv Syst*. 2018;34:1973–1988.
24. Preuner S, Lion T. Towards molecular diagnostics of invasive fungal infections. *Expert Rev Mol Diagn*. 2009;9:397–401.
25. Lackner H, Sovinz P, Benesch M, et al. Management of brain abscesses in children treated for acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2009;52:408–411.
26. Carter JH, Lenahan JL, Ishak GE, et al. Medical management of invasive fungal infections of the central nervous system in pediatric cancer patients. *Pediatr Blood Cancer*. 2015;62:1095–1098.
27. Nadkarni T, Goel A. Aspergilloma of the brain: an overview. *J Postgrad Med*. 2005;51(suppl 1):S37–S41.
28. Lin SJ, Schranz J, Teutsch SM. Aspergillosis case-fatality rate: systematic review of the literature. *Clin Infect Dis*. 2001;32:358–366.
29. Porto L, You SJ, Attarbaschi A, et al. Invasive mold infection of the central nervous system in immunocompromised children. *J Fungi (Basel, Switzerland)*. 2020;6:226.
30. Kullberg BJ, Arendrup MC. Invasive candidiasis. *N Engl J Med*. 2015;373:1445–1456.
31. Celkan T, Kizilocak H, Evim M, et al. Hepatosplenic fungal infections in children with leukemia-risk factors and outcome: a multicentric study. *J Pediatr Hematol Oncol*. 2019;41:256–260.
32. Mourad A, Perfect JR. Tolerability profile of the current antifungal armoury. *J Antimicrob Chemother*. 2018;73(suppl 1): i26–i32.
33. Moen MD, Lyseng-Williamson KA, Scott LJ. Liposomal amphotericin B: a review of its use as empirical therapy in febrile neutropenia and in the treatment of invasive fungal infections. *Drugs*. 2009;69:361–392.

34. Schwartz S, Thiel E. Cerebral aspergillosis: tissue penetration is the key. *Med Mycol*. 2009;47(suppl 1):S387–S393.
35. McCarthy M, Rosengart A, Schuetz AN, et al. Mold infections of the central nervous system. *N Engl J Med*. 2014;371:150–160.
36. Kebudi R, Kızılocak H, Hafız G, et al. Successful outcome of mucormycosis in a child with acute lymphoblastic leukemia. *Turk Pediatri Arsivi*. 2020;55:207–209.
37. Ruhnke M, Schwartz S. Recent developments in the management of invasive fungal infections in patients with oncohematological diseases. *Ther Adv Hematol*. 2016;7:345–359.
38. Jensen TSR, Arendrup MC, von Buchvald C, et al. Successful treatment of rhino-orbital-cerebral mucormycosis in a child with leukemia. *J Pediatr Hematol Oncol*. 2017;39:e211–e215.
39. Dworsky ZD, Bradley JS, Brigger MT, et al. Multimodal treatment of rhinocerebral mucormycosis in a pediatric patient with relapsed pre-B acute lymphoblastic leukemia. *Pediatr Infect Dis J*. 2018;37:555–558.
40. Schwartz S, Reisman A, Troke PF. The efficacy of voriconazole in the treatment of 192 fungal central nervous system infections: a retrospective analysis. *Infection*. 2011;39:201–210.
41. West KA, Gea-Banacloche J, Stroncek D, et al. Granulocyte transfusions in the management of invasive fungal infections. *Br J Haematol*. 2017;177:357–374.
42. Sharma RR. Fungal infections of the nervous system: current perspective and controversies in management. *Int J Surg*. 2010;8:591–601.
43. Patterson TF, Thompson GR III, Denning DW, et al. Practice Guidelines for the Diagnosis and Management of Aspergillosis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;63:e1–e60.
44. Lauten M, Attarbaschi A, Cario G, et al. Invasive mold disease of the central nervous system in children and adolescents with cancer or undergoing hematopoietic stem cell transplantation: analysis of 29 contemporary patients. *Pediatr Blood Cancer*. 2019;66:e27806.
45. Lehrnbecher T, Phillips R, Alexander S, et al. Guideline for the management of fever and neutropenia in children with cancer and/or undergoing hematopoietic stem-cell transplantation. *J Clin Oncol*. 2012;30:4427–4438.