

CNS infections in patients with hematological disorders (including allogeneic stem-cell transplantation) – Guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO)

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Infections of the central nervous system (CNS) are infrequently diagnosed in immunocompetent patients, but they do occur in a significant proportion of patients with hematological disorders. In particular, patients undergoing allogeneic hematopoietic stem-cell transplantation carry a high risk for CNS infections of up to 15%. Fungi and *Toxoplasma gondii* are the predominant causative agents. The diagnosis of CNS infections is based on neuroimaging, cerebrospinal fluid examination and biopsy of suspicious lesions in selected patients. However, identification of CNS infections in immunocompromised patients could represent a major challenge since metabolic disturbances, side-effects of antineoplastic or immunosuppressive drugs and CNS involvement of the underlying hematological disorder may mimic symptoms of a CNS infection. The prognosis of CNS infections is generally poor in these patients, albeit the introduction of novel substances (e.g. voriconazole) has improved the outcome in distinct patient subgroups. This guideline has been developed by the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO) with the contribution of a panel of 14 experts certified in internal medicine, hematology/oncology, infectious diseases, intensive care, neurology and neuroradiology. Grades of recommendation and levels of evidence were categorized by using novel criteria, as recently published by the European Society of Clinical Microbiology and Infectious Diseases.

Key words: guideline, central nervous system infection, immunocompromised patient, diagnosis, treatment

Introduction

Infections of the central nervous system (CNS) occur in a relevant proportion of immunocompromised patients and contribute significantly to morbidity and mortality. Only limited data are available on the clinical characteristics, optimal diagnostic procedures and treatment of CNS infections in these patients, and

studies on CNS infections frequently focused on specific causative agents or distinct patient subgroups such as recipients of allogeneic hematopoietic stem-cell transplantation (allo-HSCT) [1, 2].

This guideline focuses on patients with hematological malignancies including allo-HSCT recipients defined as ‘patients with hematological disorders’ hereafter. Patients with nonmalignant hematological disorders (e.g. aplastic anemia) or solid tumors are not specifically excluded albeit CNS infections are very rare in these patients and larger analyses focusing on CNS infections in these subgroups are lacking. In the first part of this guideline, an overview on epidemiology, causative agents, risk factors,

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Table 1. Strength of recommendation (A) and quality of evidence (B) [3]

(A)	
Grade	Strength of recommendation
Grade A	AGIHO 'strongly' supports a recommendation for use
Grade B	AGIHO 'moderately' supports a recommendation for use
Grade C	AGIHO 'marginally' supports a recommendation for use
Grade D	AGIHO 'supports' a recommendation 'against' use
(B)	
Level	Quality of evidence
I	Evidence from at least one properly designed randomized, controlled trial
II*	Evidence from at least one well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time series; or from dramatic results of uncontrolled experiments
	*: Added index
	r: Meta-analysis or systematic review of randomized, controlled trials
	t: Transferred evidence, that is, results from different patients' cohorts, or similar immune-status situation
	h: Comparator group is a historical control
	u: Uncontrolled trial
	a: Published abstract (presented at an International Symposium or meeting)
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies

Quality of evidence is used for treatment recommendations only (and not for diagnostic procedures).

pathogenesis, prophylaxis in addition to general diagnostic strategies and management of CNS infections is given. The second part focuses on distinct infectious agents. For recommendations on diagnosis and treatment of bacterial CNS infections (including tuberculous meningitis), see supplementary Material, available at *Annals of Oncology* online. The strengths of recommendation and levels of evidence were categorized according to the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) criteria (Table 1) [3].

consensus process

See supplementary Material, available at *Annals of Oncology* online.

epidemiology and causative agents

Patients undergoing allo-HSCT are among those with the highest risk for CNS infections with an overall incidence of up to 15% [1, 4, 5]. *Aspergillus* and *Toxoplasma* spp. are frequently prevailing in these patients [4, 6]. Patients after an alemtuzumab-based conditioning before allo-HSCT carry a considerable risk for viral CNS infections [2, 7]. Mucormycosis is diagnosed in ~0.1% of all patients with hematological disorders, but an increased incidence (1.0%–1.9%) has been reported among patients with acute myeloid leukemia [8]. The lungs are frequently infected in mucormycosis, but the CNS might be involved in 10%–20% of patients [9, 10]. Progressive multifocal leukoencephalopathy (PML) is a rare (<1%), but frequently fatal CNS disease caused by the JC virus. It mainly affects allo-HSCT recipients, but also patients after rituximab-based treatment strategies or with multiple lines of immunosuppression [2, 11, 12]. Bacterial CNS infections are rarely diagnosed in patients with hematological disorders, and they occur more frequently in patients with intraventricular devices or after neurosurgical interventions [1, 13–15].

pathogenesis

See supplementary Material, available at *Annals of Oncology* online.

prophylaxis

Prophylactic strategies should follow recommendations for immunocompromised patients as published elsewhere [16, 17]. Patients with hematological disorders requiring intracerebral devices such as an external ventricular drainage could benefit from antimicrobial-impregnated catheters since they might be associated with a lower infection rate in comparison to standard catheters [15].

general strategies to diagnose and to treat CNS infections in patients with hematological disorders

Some principal aspects regarding the management of CNS infections in patients with hematological disorders should be considered:

- (i) The management of CNS infections in patients with hematological disorders requires a high level of awareness, as neurological symptoms could be nonspecific and caused by noninfectious conditions related to the underlying disease and/or side-effects of antineoplastic or immunosuppressive treatment [1, 5, 14].
- (ii) While clinical presentations of CNS infections in immunocompetent hosts are broadly categorized into meningitis, meningoencephalitis, cerebritis/abscess formation and infection of intracerebral devices, diminished inflammatory responses in immunocompromised patients can lead to only subtle symptoms. Mass lesions can be blurred by rather nonspecific cerebral dysfunctions such as confusion or altered consciousness [1, 14].

- (iii) Defined patient groups predispose for infections with certain pathogens based on their pattern of immunosuppression (defects in cell-mediated immunity versus defective humoral immunity) [18, 19]. Bacterial, fungal and viral CNS infections typically occur in neutropenic patients. Defects in T-cell immunity or in function of macrophages predispose for cerebral toxoplasmosis and cryptococcal meningitis [2, 18, 20].
- (iv) Variations in the frequency of causative organisms (e.g. *Toxoplasma* spp. *Histoplasma capsulatum*, *Mycobacterium tuberculosis*) due to regional endemic differences should be taken into account [21–23].

diagnosis

Any suspicion of CNS infection should immediately trigger adequate diagnostic procedures including neuroimaging, cerebrospinal fluid (CSF) examination and, in selected cases, biopsy of focal lesions (Figure 1). CSF analyses including various methods such as staining and microscopy, culturing, serological techniques and PCR assays are crucial to diagnose meningoencephalitis which is typically caused by viruses, *Candida* spp., bacteria or more rarely *Cryptococcus* spp. (Figure 1, Table 2). For these CNS infections, brain biopsy is required only in selected cases. Focal

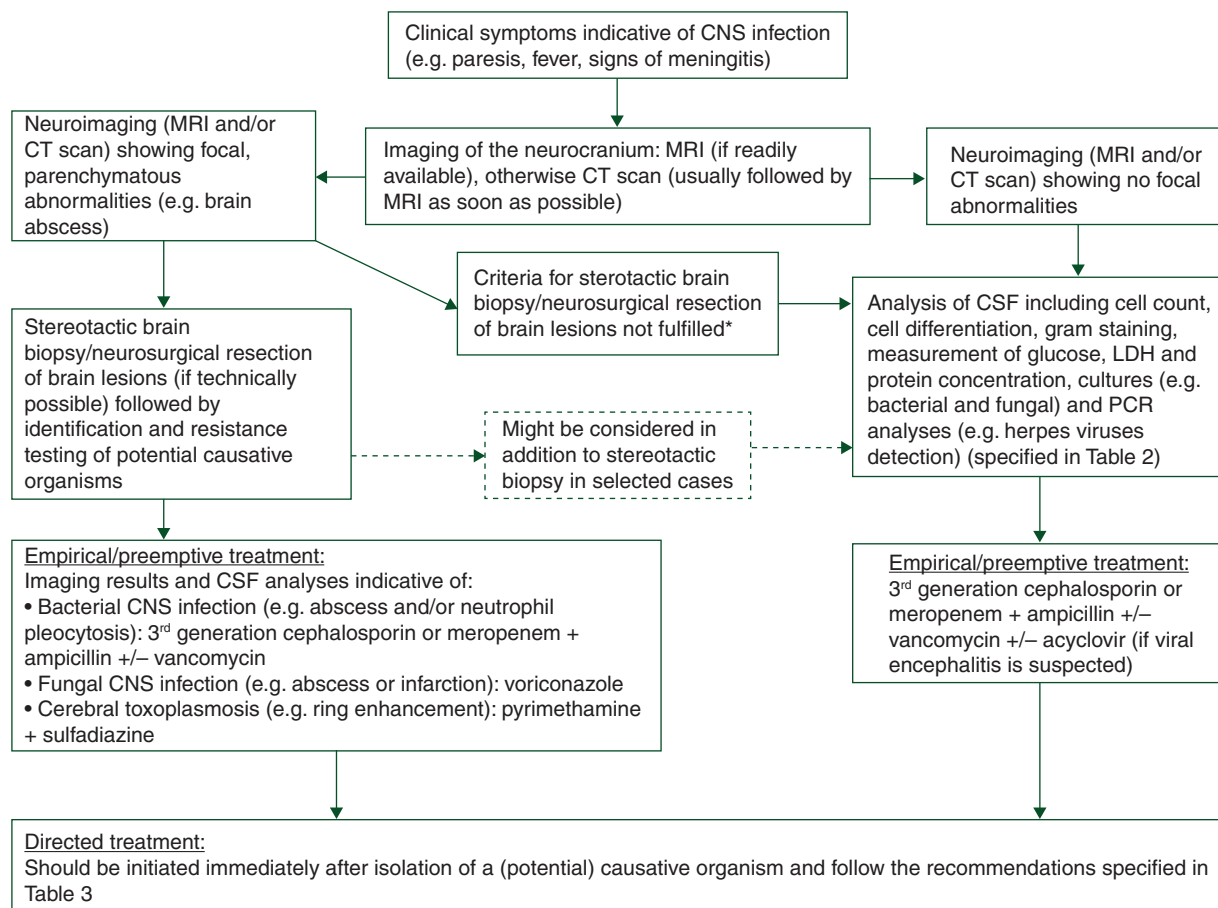
lesions, typically caused by *Toxoplasma* or *Aspergillus* spp. are commonly diagnosed by histopathology of suspicious lesions. Histopathological work-up should be done using adequate staining methods such as Calcofluor white. Routine parameters in the CSF are frequently nonspecifically altered in these patients.

Neuroimaging should commonly be based on magnetic resonance imaging (MRI) since it is more sensitive than computed tomography (CT) scan for diagnosis of the majority of CNS infections [102–105].

Further diagnostic methods such as positron emission tomography might help in selected patients to differentiate infectious from noninfectious CNS lesions [106].

antimicrobial treatment

Given the dismal outcome of delayed treatment in patients with hematological disorders and CNS infection, antimicrobial treatment should be initiated promptly once collection of CSF and blood cultures has been completed (Figure 1) [107–109]. After isolation and *in vitro* susceptibility testing of a (potentially) causative pathogen, antimicrobial treatment should be modified accordingly. Recommendations for empiric, pre-emptive and targeted treatment are specified in Figure 1, Table 3 and supplementary Table S1, available at *Annals of Oncology* online.



*The decision on brain biopsy/neurosurgical resection should always be made on the basis of the technical feasibility, the suspicious causative agent, and other factors (such as presence of thrombocytopenia). For example, brain biopsy might not be required to establish the diagnosis of PML in patients with typical neuroimaging findings together with a positive CSF JC virus PCR.

Figure 1. Diagnostic procedures and management in patients with hematological disorder and CNS infection.

Table 2. Recommendations to diagnose CNS infections in patients with hematological disorders

Intention	Intervention	SoR	Comments	References
<i>Toxoplasma</i> spp.				
To diagnose cerebral toxoplasmosis	Demonstration of tachyzoites and/or cysts after Wright-Giemsa and/or immuno-peroxidase staining (CSF or biopsy material)	A	Can be combined with isolation of the parasite, e.g. after mouse inoculation or inoculation in tissue cell cultures	[24]
	PCR (CSF)	B	Sensitivity 50%–100%, specificity 90%–100%. Should be performed within the first week after initiation of antitoxoplasmic treatment	[25–28]
	IgG-ELISA/LAT (CSF)	C	IgG-ELISA is more sensitive than LAT (92% versus 48%)	[29]
	IgM-ELISA (CSF)	D	Negligible value	[29]
	LAMP assay (CSF)	D	Few data	[25]
Fungi				
To detect and specify a fungus obtained from CNS biopsy	Paraffin sections of CNS biopsies (e.g. using H&E, PAS, or Grocott/silver stains)	A	Might not always be possible (e.g. in patients with thrombocytopenia). Thus, biopsy of lesions from anatomic sites other than CNS might be considered sufficient to establish the diagnosis	[30, 31]
To diagnose CNS aspergillosis	Detection of galactomannan (CSF)	B	No validated cutoff (probably lower than for serum samples), reduced sensitivity under antifungal treatment	[32–36]
	PCR (CSF)	B	Sensitivity and specificity 90%–100% (in-house assays)	[33, 37–41]
	Fungal cultures (CSF)	B	Positive in ~30% of patients with <i>Aspergillus</i> meningitis	[32, 36]
To diagnose <i>Candida</i> CNS infection	Detection of (1→3)-β-D-glucan (CSF)	C	Few data	[42, 43]
	Microscopy/culture (CSF)	A	Sensitivity of microscopy ~40%, of culture 40%–80%	[44, 45]
	CNS biopsy (culture/histopathology)	B	If biopsy can be achieved (e.g. using Grocott/silver stains)	[44, 45]
	Detection of <i>Candida</i> mannan antigen (CSF)	C	Few data	[46–48]
	Detection of (1→3)-β-D-Glucan (CSF)	C		[43, 49]
To diagnose mucormycosis	PCR (CSF)	C		[38, 50–52]
	CNS/extracerebral tissue biopsy (culture/histopathology)	A	Useful stains: PAS, Grocott/silver stains, Calcofluor white	[53]
	PCR (tissue)	B	Few data	[54–56]
	PCR (blood)	C		[57]
To diagnose cryptococcal meningitis	CSF-based diagnostics	D	No valid data	
	Culture (CSF)	A	Sensitivity 60%–100%, specificity near 100%	[58–61]
	CSF microscopy (e.g. after India Ink staining)	A	Sensitivity 70%–95%, specificity near 100%; often operator-dependent	[58, 59, 61, 62]
	Detection of capsular antigen, e.g. by EIA, LAT or LFA (CSF)	A	Sensitivity and specificity 90%–100%	[58, 60, 61, 63]
	(Nested) PCR (CSF)	B	Sensitivity and specificity near 100%	[58–61]
Viruses	Biopsy (culture/histopathology), e.g. after Grocott/silver or Alcian blue staining	C	Required only in selected cases	[60]
	To diagnose HSV encephalitis			
	PCR (CSF)	A	Sensitivity and specificity 95%–100%	[64, 65]
	Detection of HSV antigens and antibodies (CSF)	C	Sensitivity and specificity of HSV antigen detection ~90%, frequently nonspecific antibodies	[66, 67]
	Culture (CSF)	D	Low sensitivity of culture might be due to inhibiting HSV IgG antibodies	[66, 68, 69]
To diagnose CMV CNS disease	PCR (CSF)	A	Sensitivity nearly 100%	[70–72]
	Culture (CSF)	C	Might only be used as an adjunctive test (sensitivity ~20%)	[69, 72]
To diagnose EBV meningoencephalitis	PCR (CSF)	A	Might be false-negative in allo-HSCT recipients	[2, 73–76]

To diagnose HHV-6 meningoencephalitis	PCR (CSF)	A	Might be positive in allo-HSCT recipients without associated symptoms	[77–79]
To diagnose VZV CNS disease	PCR (CSF)	A		[80–82]
	Detection of VZV IgG antibodies (CSF)	B	Might be more sensitive than CSF VZV PCR in the case of cerebral VZV vasculopathy	[83–85]
To diagnose JC virus-related PML	Biopsy of CNS lesions	A	Required for definitive diagnosis, demonstration of the typical triad including demyelination, bizarre astrocytes and enlarged oligodendroglial nuclei	[86, 87]
	PCR (CSF)	A	Sensitivity 75%–100%, repetitive CSF analyses might be useful, might also be false-positive (e.g. in healthy individuals with JC virus viremia)	[86, 88–90]
Bacteria				
To identify pathogen and perform resistance testing	Culture (CSF)	A	CSF culture yield might significantly be reduced in patients with delayed lumbar puncture (>4 h) after initiation of antibiotic treatment	[91–93]
	Culture (blood)	A	Positive in 50%–80% of patients, after initiation of antibiotic treatment in ~20%	[92, 94]
To identify bacteria in culture-negative CSF specimens	Gram stain (CSF)	A	Sensitivity 30%–93%, specificity 97% (frequently still positive after initiation of antibiotic treatment)	[91, 94, 95]
To document bacterial meningoencephalitis versus meningoencephalitis of other origin	Counting and differentiation of CSF cells	A	Might be of inferior value in neutropenia or after initiation of antibiotic treatment	[14, 92, 96, 97]
	Determination of CSF LDH concentration	B		[98]
	Determination of CSF protein and glucose concentration	C		[14, 92, 96, 97]
To identify causative bacterial agent in meningoencephalitis	CSF PCR	B		[99–101]

SoR, strength of recommendation; ELISA, enzyme-linked immunosorbent assay; LAT, latex agglutination test; LDH, lactate dehydrogenase; LAMP, loop-mediated isothermal amplification; H&E, hematoxylin and eosin; PAS, periodic acid-Schiff; EIA, enzyme immunoassay; LFA, lateral flow immunochromatographic assay.

Table 3. Recommendations to treat CNS infections in patients with hematological disorders^a

Causative agent	Intention	Intervention	SoR/QoE	Comments	References
<i>Toxoplasma</i> spp.					
<i>Toxoplasma</i> spp.	Primary anti-infective treatment and prevention of CNS relapse - to cure -	Pyrimethamine (orally, 100–200 mg load, then 50 mg/day) + sulfadiazine (orally, 1 g q6h)	AII _t	Anti-infective agents should be given for ~6 weeks in indicated dosages, then as maintenance therapy half of the original dosage for at least 3 months Pyrimethamine should be combined with folinic acid	[110]
		Pyrimethamine (orally, 100–200 mg load, then 50 mg/day) + clindamycin (orally or i.v., 600 mg q6h)	BII _t		[111–113]
		Trimethoprim (10 mg/kg/day)—sulfamethoxazole (orally or i.v.)	BII _t		[114]
		Atovaquone (orally, e.g. 750 mg q6h)	BII _{t,u}	Might be used for maintenance in patients intolerant to conventional antitoxoplasmic agents, could be combined as primary treatment with pyrimethamine or sulfadiazine	[115, 116]
Fungi					
<i>Aspergillus</i> spp.	Primary anti-infective treatment ^b - to cure -	Voriconazole (i.v., 6 mg/kg q12h for the first 24 h, then 4 mg/kg q12h)	AII _u		[117, 118]
		-To obtain material for diagnosis	L-AmB (i.v., ≥5 mg/kg/day, optimal dose unclear) or ABLC ^c (i.v., 5 mg/kg/day)	BIII	Reserved for rare cases (e.g. severe intolerance to voriconazole, resistant isolates), might in particular be useful if mucormycosis cannot be excluded
	-To prevent serious neurological sequelae, decrease the burden of infected tissue and improve outcome	Itraconazole	DIII	Higher doses (800 mg/day) might be beneficial, low CNS penetration	[127–129]
		Caspofungin, micafungin	DIII	Few clinical data	[130, 131]
		Posaconazole	DIII		[132, 133]
		D-AmB	DII _u	Unfavorable toxicity profile, low efficacy	[134, 135]
		Stereotactic or open craniotomy for biopsy, abscess drainage or excision of lesions	BII _u	Resection might be effective in particular in patients with a focal lesion, a combined neuro- and rhinosurgical approach is recommended in selected cases	[117–119, 136–139]
<i>Candida</i> spp.	Primary anti-infective treatment ^b - to cure -	L-AmB (i.v., ≥5 mg/kg/day, optimal dose unclear) or ABLC ^c (i.v., 5 mg/kg/day) ± 5-FC (i.v., 25 mg/kg q6h) ^d	BIII	Mainly preclinical data, case reports or small patient series (and data from extracerebral systemic <i>Candida</i> infection)	[140–144]
		Voriconazole (i.v., 6 mg/kg q12h for the first 24 h, then 4 mg/kg q12h)	CIII		[145, 146]
		Fluconazole (i.v., loading dose 800 mg/day, then 400 mg/day)	CIII	If a susceptible <i>Candida</i> spp. has been isolated and the patient is clinically stable and not neutropenic and had no prior azole exposure	[44, 141, 147–149]
		D-AmB	DIII	Unfavorable toxicity profile	[44, 135, 147, 149, 150]
		Caspofungin, micafungin, anidulafungin	DIII	Mainly preclinical data and few case reports	[151–153]

<i>Mucorales</i>	Primary treatment - to cure -	Surgery	AII _{t,u}	Should be considered whenever possible	[8, 9, 154, 155]	
		L-AmB (i.v., ≥5 mg/kg/day, optimal dose unclear, up to 10 mg/kg/day has been used)	AII _{t,u}	Treatment delay may enhance mortality, response rate 80%–95%	[10, 155, 156]	
		Reduction of immunosuppression	BIII	No comparative data, not always feasible		
		ABL ^C (i.v., 5 mg/kg/day)	BIII	Around 70% response rate	[157]	
		L-AmB (i.v., ≥5 mg/kg/day) + caspofungin (i.v., 50–70 mg/day)	CIII		[158–163]	
		Posaconazole (preferable i.v., 300 mg q12h for the first 24 h, then 300 mg/day)	CIII	Low CNS penetration, dosages up to 3200 mg/day have been used	[156, 164]	
		Posaconazole (preferable i.v., 300 mg q12h for the first 24 h, then 300 mg/day) + L-AmB (i.v., ≥5 mg/kg/day)	CIII	Might be used for extended cases or patients refractory to single-agent treatment	[156, 161, 164–166]	
		Itraconazole (orally or i.v., higher dosages of up to 800 mg/day might be used)	CIII	Low CNS penetration	[9]	
		D-AmB	DIII	Unfavorable toxicity profile	[9, 135]	
		Salvage treatment - to cure/prolong survival -	Posaconazole (preferable i.v., 300 mg q12h for the first 24 h, then 300 mg/day)	BIII	Might be combined with caspofungin or L-AmB	[164, 167, 168]
Isavuconazole (i.v. or orally, 200 mg q8h for the first 48 h, then 200 mg/day)	CIII			[169, 170]		
<i>Cryptococcus</i> spp.	Primary treatment - to cure -	L-AmB (i.v., 3–4 mg/kg/day) or ABL ^C (i.v., 5 mg/kg/day) + 5-FC (i.v., 25 mg/kg q6h) ^d	AII _t	• Induction therapy for at least 4 weeks, might be followed by consolidation with fluconazole (400 mg/d) at least 8 weeks	[171–173]	
		D-AmB (i.v., 0.7–1.0 mg/kg/day) + 5-FC (i.v., 25 mg/kg q6h) ^d	BII _t	• Consider unfavorable toxicity profile of D-AmB	[171–174]	
		D-AmB (i.v., 0.7–1.0 mg/kg/day) + voriconazole (preferable i.v., 6 mg/kg q12h for the first 24 h, then 4 mg/kg q12h)	BII _t		[175]	
		L-AmB (i.v., 3 mg/kg/day)	BII _t		[176–178]	
		D-AmB (i.v., 0.7–1.0 mg/kg/day) + fluconazole (preferable i.v., 800–1200 mg/day)	CII _t		[171, 173, 175, 179]	
		Voriconazole (preferable i.v., 6 mg/kg q12h for the first 24 h, then 4 mg/kg q12h)	CIII		[180]	
		ABL ^C (i.v., 5 mg/kg/day)	CIII		[181]	
		Fluconazole (preferable i.v., loading dose 1200 mg/day, then 800 mg/day) + 5-FC (i.v., 25 mg/kg q6h) ^d	CII _t	Study performed in Malawi with limited economic resources	[182]	
		Salvage treatment - to cure/prolong survival -	Voriconazole (preferable i.v., 6 mg/kg q12h for the first 24 h, then 4 mg/kg q12h)	CIII	Clinical efficacy rate ~40%	[183]
			Posaconazole (preferable i.v., 300 mg q12h for the first 24 h, then 300 mg/day)	CIII	Clinical efficacy rate ~50%	[132]
Primary or salvage treatment	Caspofungin, micafungin, anidulafungin	DIII	No relevant activity	[184]		

Viruses

Continued

Table 3. *Continued*

Causative agent	Intention	Intervention	SoR/QoE	Comments	References
HSV	Primary or salvage treatment - to cure -	Aciclovir (i.v., 10 mg/kg q8h)	AII _t	Treatment duration at least 2–3 weeks ^e	[2, 73, 185–189]
		Foscarnet (i.v., 60 mg/kg q8h or 90 mg/kg q12h)	CIII	Might be used in refractory cases	[190]
CMV	Primary or salvage treatment - to cure -	Valaciclovir (orally, 1 g q8h)	CIII	Might be used as continuation therapy	[191–194]
		Ganciclovir (i.v., 5 mg/kg q12h) or foscarnet (i.v., 60 mg/kg q8h or 90 mg/kg q12h) as single agent	AIII	Consider main side-effects (myelotoxicity versus nephrotoxicity) and the presence of CMV resistance mutations (e.g. UL97, UL54)	[188]
		Ganciclovir (i.v., 5 mg/kg q12h) + foscarnet (i.v., 60 mg/kg q8h or 90 mg/kg q12h)	BIII		[188, 195–197]
		Cidofovir (i.v., optimal dosage unclear, e.g. 5 mg/kg once weekly)	CIII		[198, 199]
		Ganciclovir (i.v., 5 mg/kg q12h) + cidofovir (i.v., e.g. 5 mg/kg once weekly)	CIII		[195, 200]
EBV (meningoencephalitis)	Primary or salvage treatment - to cure -	Foscarnet (i.v., 60 mg/kg q8h or 90 mg/kg q12h) + ganciclovir (i.v., 5 mg/kg q12h)	CIII		[195, 201]
		Reduction of immunosuppression	AIII	Might not always be possible	[188, 202]
HHV-6	Primary or salvage treatment - to cure -	Ganciclovir (i.v., 5 mg/kg q12h)	BIII	Valganciclovir (orally) has also been used	[202–207]
		Aciclovir (i.v., 10 mg/kg q8h)	CIII	Few reports with success published	[208, 209]
		Foscarnet (i.v., 60 mg/kg q8h or 90 mg/kg q12h) or ganciclovir (i.v., 5 mg/kg q12h)	AIII	Variant A and B might respond similarly to antivirals	[7, 77, 78, 210–213]
VZV	Primary or salvage treatment - to cure -	Foscarnet (i.v., 60 mg/kg q8h or 90 mg/kg q12h) + ganciclovir (i.v., 5 mg/kg q12h)	CIII		[78, 214]
		Cidofovir (i.v., e.g. 5 mg/kg once weekly)	CIII		[215]
		Aciclovir (i.v., 10 mg/kg q8h) ^f	AIII	Inefficacy has been reported	[2, 73, 216–218]
JC virus (PML)	Primary or salvage treatment - to cure -	Aciclovir (i.v., 10 mg/kg q8h) + foscarnet (i.v., 60 mg/kg q8h or 90 mg/kg q12h)	CIII		[219]
		Ganciclovir (i.v., 5 mg/kg q12h)	CIII		[188, 220]
Bacteria	To reduce mortality and neurologic defects	Reduction of immunosuppression	AIII	Not always possible	[12]
		Cidofovir	DII _{t,u}		[221]
Bacteria	To reduce mortality and neurologic defects	Empiric treatment	AII _{t,u}		[107, 222, 223]
		Dexamethasone (e.g. 0.15 mg/kg q6h for the first 4 days)	CII _{r,t}	Should be started with first dose of antibiotics if it is used	[224, 225]

<p>To reduce mortality in first-line empirical treatment</p> <p>Meropenem (2 g q8h) or ceftriaxone (2 g q12h) AII_r</p> <p>or cefotaxime (8–12 g/day in 4–6 daily dosages) + ampicillin (2 g q4h) ± vancomycin (30–60 mg/kg/day in 2–3 daily dosages)</p> <p>To reduce mortality (Gram-negative strains)</p> <p>Meropenem (2 g q8h) BIII</p>	<p>Add vancomycin if a high rate of penicillin-resistant <i>S. pneumoniae</i> strains is present [92, 226]</p> <p>Carbapenem of choice for <i>Enterobacteriaceae</i> (more potent than imipenem and ertapenem) [227, 228]</p> <p>The authors do not take any responsibility for dosages of anti-infectious agents.</p> <p>^aFor detailed recommendations on treatment of different bacterial CNS infections in patients with hematological disorders, see supplementary Material, available at <i>Annals of Oncology</i> online.</p> <p>^bAntifungal drug therapy should be continued for at least 4 weeks after resolution of all signs and symptoms of the infection.</p> <p>^cNot distributed in some countries (e.g. Germany).</p> <p>^dTherapeutic drug monitoring recommended.</p> <p>^eLonger treatment periods might be advisable (e.g. determined by repeated CSF analyses).</p> <p>^fUsual pediatric dose (immunocompromised host): 10–20 mg/kg q8h.</p> <p>QoE, quality of evidence; ABLC, amphotericin B lipid complex.</p>
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Due to the lack of systematic data, decisions about the duration of antimicrobial treatment should be assessed individually. Hereby, the strategy of treatment (such as antimicrobial drug therapy with or without surgery), resolution of symptoms and recovery of the individual immune-status, as defined by the presence of neutropenia, hypogammaglobulinemia and graft-versus-host disease should be taken in account. In patients with persisting complex immunodeficiencies, targeted antimicrobial treatment might be followed by maintenance treatment (e.g. for cerebral toxoplasmosis). To improve efficacy and minimize toxicity, therapeutic drug monitoring (TDM) might be useful for antimicrobial agents, such as 5-fluorocytosine (5-FC), voriconazole and posaconazole [BII] [229, 230]. TDM might be of particular relevance in patients with hematological disorders since impaired gastrointestinal resorption and interferences with co-medication are common in this population [230–232].

adjunctive treatment

Adjunctive treatment may include neurosurgery, platelet transfusion and administration of corticosteroids, anticonvulsants, sedatives or antipyretics (see supplementary Material, available at *Annals of Oncology* online).

CNS infections related to specific causative agents

parasitic CNS infections

Toxoplasma spp. belong to the most common causative agents in allo-HSCT recipients with CNS infections [1, 6]. However, other parasitic CNS infections such as malaria, microsporidiosis, leishmaniasis, trypanosomiasis or helminthic infections have also been described in immunocompromised hosts [233].

Toxoplasma spp. Mental abnormalities, fatigue and fever are frequent clinical symptoms in allo-HSCT recipients with cerebral toxoplasmosis [234]. Neuroimaging by MRI frequently shows typical hypo-/isointensities mainly in the basal ganglia and the frontal lobe (supplementary Figure S1, available at *Annals of Oncology* online) [105]. Higher sensitivity of MRI compared with CT scan has been demonstrated in a comparative retrospective analysis [104, 105]. However, typical nodular or ring enhancement surrounded by edema was visible by MRI in only 60% of allo-HSCT patients [235]. Besides neuroimaging, diagnosis of cerebral toxoplasmosis is based on demonstration of tachyzoites or cysts in the CSF [A], CSF PCR [B] and serological tests such as CSF enzyme-linked immunosorbent assay [C] [24, 25, 29].

Primary treatment of cerebral toxoplasmosis should comprise a combination of pyrimethamine and sulfadiazine [AII_r] [110]. Pyrimethamine in combination with clindamycin [BII_r] or single-agent trimethoprim-sulfamethoxazole [BII_r] may alternatively be used [110, 111, 236]. Maintenance treatment should be conducted for at least 3 months [BIII]. Atovaquone could be administered in patients with intolerance/refractoriness to conventional antitoxoplasmic agents [BII_{t,u}] [115, 116].

fungi

The predominant fungal pathogens causing CNS infections in patients with hematological disorders are *Aspergillus* spp., with

A. fumigatus prevailing over other species such as *A. nidulans*, *A. terreus* and *A. flavus* [117]. *Mucorales*, *C. neoformans* and *Candida* spp. may also be detected in these patients [150].

Aspergillus spp. Most commonly, CNS *Aspergillosis* results in brain abscess formation, but fungal embolism can also cause cerebral infarction with or without hemorrhage. Rarely, CNS aspergillosis presents with overt meningitis or cause granuloma [32, 150, 237].

MRI may show ring-enhanced lesions, infarction and dural or vascular infiltration from adjacent regions (supplementary Figure S2, available at *Annals of Oncology* online) [238, 239]. A definitive diagnosis frequently requires biopsy of suspicious lesions and demonstration of typical septate hyphae [A] [30, 31]. Several studies indicate that detection of CSF galactomannan [B] or the PCR assay [B] might also be useful to diagnose CNS aspergillosis [32–35, 37]. In *Aspergillus* meningitis, CSF galactomannan might be detected in almost 90% of cases, whereas fungal cultures are positive in ~30% [32]. CSF fungal cultures are usually negative in patients with *Aspergillus* CNS infection other than meningitis [32].

Voriconazole is the drug of choice in CNS aspergillosis, as this azole displays sufficient penetration into the CNS [AII_u] [117, 118, 240]. Amphotericin B deoxycholate (D-AmB) should be avoided due to its poor tolerability and negligible efficacy [DII_u], but the use of higher doses of liposomal AmB (L-AmB) resulted in successful outcomes in a limited number of patients [BIII] [119–123, 134]. Due to its limited CNS penetration and the limited number of successfully treated cases in the literature, the use of itraconazole does not appear justifiable in patients with CNS aspergillosis [DIII] [127–129]. Posaconazole has been used in a series of patients with CNS infections caused by various fungi, including three assessable patients with CNS aspergillosis [DIII] [132]. Caspofungin has demonstrated some activity in a mouse model exploring CNS aspergillosis, but clinical data on the use of echinocandins in CNS aspergillosis are scarce [130, 131]. Some animal model data suggest that combination therapy (e.g. voriconazole with L-AmB) might be beneficial, but meaningful clinical data are not available to recommend the use of combination therapies in CNS aspergillosis [DIII] [241, 242].

Intrathecal or intralesional administration of AmB has been repeatedly been applied to patients with CNS aspergillosis, but published data are limited to case reports [DIII] [243, 244]. In addition, intrathecal D-AmB could cause chemical arachnoiditis and it is unlikely that sufficient drug concentration is achieved in infected brain tissues [245]. Adjunctive corticosteroid therapy could reduce mass effects and brain edema, but should be avoided whenever possible due to its deleterious effects in invasive fungal infections [246]. If corticosteroid therapy is unavoidable, prednisolone should be preferred over dexamethasone, as dexamethasone is associated with low voriconazole levels (S. Schwartz, personal communication).

Neurosurgical interventions could facilitate diagnostic confirmation and contribute to a successful outcome, likely by removing infarcted areas with poor drug penetration [BII_u] [117, 118, 136, 137].

Candida spp.. *Candida* CNS infections typically present as meningoencephalitis or as ventriculitis associated with foreign

bodies such as shunts or, rarely, as brain abscesses. *Candida* microabscesses could be discovered at autopsy, while CT and CSF analysis not always show clearly pathological findings in this situation [44]. Neuroimaging might show hydrocephalus in *Candida* meningitis and MRI is considered to be more sensitive than CT scan [44, 147]. In the case of *Candida* meningitis, yeasts can be detected by CSF staining in ~40% and in ~40%–80% by fungal cultures [A] [44, 45]. The PCR technique as well as the detection of (1 → 3)-β-D-Glucan or the *Candida* mannan antigen might also be useful to diagnose *Candida* meningitis from CSF, but these methods are not yet considered as clinical routine procedures [C] [38, 46, 47, 49].

Most data on the treatment of *Candida* CNS infection are derived from pediatric patients. The use of D-AmB with 5-FC has been suggested as the optimal initial therapy for many years due to the excellent CSF penetration of 5-FC, the documented synergism of both compounds *in vitro* and *in vivo* and their documented clinical activity in *Candida* infections [44, 150]. The rationale for the use of L-AmB is mainly reasoned by studies in experimental *Candida* meningoencephalitis and clinical data from preterm newborns [140, 141, 247, 248]. Since L-AmB has an improved toxicity profile compared with D-AmB, the combination of L-AmB and 5-FC should be preferred to treat *Candida* CNS infections [BIII]. Fluconazole, alone or in combination with 5-FC, may be used as an oral consolidation therapy [BIII]. Voriconazole is a reasonable therapeutic option for *Candida* CNS infection [CIII] [145, 249]. Animal models suggest the potential usefulness of the echinocandins in *Candida* CNS infection, although higher doses might be required (as studied for micafungin) [151]. Clinical data are limited to case reports; thus this approach cannot be recommended for routine use yet [DIII] [152]. Any indwelling device such as a ventricular drain or a central venous line should be removed in invasive *Candida* infection [BIII] [250, 251].

mucorales. Mucormycosis is a rare opportunistic infection mainly caused by *Rhizopus* spp. and *Mucor* spp. [9, 156]. The brain might be involved in a disseminated infection or by infiltration from adjacent rhino-sinu-orbital regions [8–10, 154, 156]. Clinical symptoms such as facial pain or swelling may be nonspecific but are frequently present in patients with rhinocerebral mucormycosis [158]. The CT scan frequently reveals characteristic bone destruction of the paranasal sinuses, the hard palate or adjacent structures [252]. The diagnosis should always be confirmed by a histopathological examination and/or culturing of tissue specimens [A]. Histopathological examination of infected tissue typically shows the irregular fungal hyphae with wide-angle branching, in addition to tissue necrosis and fungal angioinvasion [53]. PCR assays using infected tissue specimens [B] or blood [C] have also been evaluated to diagnose mucormycosis [54, 55, 57]. However, these methods are not standardized yet.

Single-agent L-AmB is recommended to treat mucormycosis [AII_{t,u}], but some experts suggest a primary polyene–caspofungin combination [CIII] [158–160]. Immediate surgical resection of necrotic tissue may be crucial in addition to antifungal treatment in invasive mucormycosis [AII_{t,u}] [8, 9, 154, 155]. Besides reduction of immunosuppressive drugs conditions associated with the occurrence of mucormycosis such as hyperglycemia,

lactic acidosis and iron overload should be corrected whenever possible [BIII]. However, a placebo-controlled trial exploring L-AmB together with the iron chelating agent deferasirox was terminated prematurely due to inefficacy, despite the crucial role of iron in the pathogenesis of mucormycosis [DII_t] [253]. Posaconazole [BIII] or isavuconazole [CIII] might be used as salvage treatment of mucormycosis [167–170]. Hyperbaric oxygen has been investigated as primary or salvage treatment of mucormycosis [254–256]. This approach is available only in some centers and there are no larger trials confirming its benefit [CIII].

Cryptococcus spp. Reports from human immunodeficiency virus (HIV)-negative patients with hematological disorders and infection with *Cryptococcus spp.* are limited [257, 258]. Neuroimaging by MRI may show dilated Virchow-Robin spaces, cyst-like structures and granuloma of the choroid plexus [259]. A definitive diagnosis of cryptococcal meningitis is made by CSF cultures [A] or CSF microscopy using India Ink staining [A] [58–60, 62]. The diagnosis might further be confirmed by detection of capsular antigen using different techniques such as enzyme immune assays, latex agglutination or the lateral flow assay [A] [58, 61]. Likewise, CSF (nested) PCR assays might be used to diagnose cryptococcal meningitis [B] [58, 61]. Biopsy of infected tissues followed by culturing and histopathological investigation is required only in selected cases [C] [60].

Primary treatment of cryptococcal meningitis should encompass a combination of L-AmB and 5-FC [AII_t] [171, 172, 181, 260]. Voriconazole or posaconazole may be used for salvage treatment [CIII] [132, 180, 183]. *Cryptococcus spp.* are *in vitro* resistant to echinocandins [184]. Thus, these agents do not play a role in the treatment of cryptococcal meningitis [DIII]. Reducing the CSF opening pressure (e.g. by repetitive lumbar punctures) is useful besides anti-infectious drug therapy in selected patients with cryptococcal meningitis [BII] [172, 261].

viruses

Herpes viruses, in particular herpes simplex virus (HSV), Epstein-Barr virus (EBV) and human herpes virus-6 (HHV-6) are prevailing in allo-HSCT recipients [2, 73]. Viral CNS infections typically present as meningoencephalitis, but strokes—e.g. caused by varicella zoster virus (VZV)—or leukoencephalopathy (e.g. JC virus-associated PML) might occur [18]. The diagnosis of viral CNS infections is usually made by CSF PCR together with neuroimaging, preferably MRI [2, 109, 262].

CSF viral PCR assays have an excellent sensitivity and specificity of 90%–100% for the majority of virus types [64, 65]. Thus, CSF PCR is regarded as a 'gold standard' for diagnosis of viral CNS infections [A]. However, studies comparing viral isolation from autopsy samples or brain-biopsy specimens—the former reference standard—with PCR are available only for few viruses such as HSV or cytomegalovirus (CMV) [64, 65, 70]. CSF virus PCR might initially be false-negative and the probability of a positive PCR increases when there is a time frame of 3–14 days between onset of symptoms and lumbar puncture [263].

herpes simplex virus. The incidence of HSV encephalitis is relatively low in patients with hematological disorders and there

have been few cases published which mainly include allo-HSCT recipients [2, 73, 264].

CSF PCR is a rapid method to diagnose HSV encephalitis with high sensitivity and specificity (both >90%) [A] [64, 65]. Detection of CSF HSV antibodies is not a reliable diagnostic tool for HSV encephalitis since the sensitivity and specificity is only 75%–85% and 60%–90%, respectively [C] [66]. Detection of CSF HSV antigen has a sensitivity and a specificity of ~90% and might be of value as an adjunctive test [C] [66, 67]. CSF viral cultures are frequently negative in HSV encephalitis [D] [68]. Cerebral MRI typically shows abnormalities in the medial and inferior temporal lobe, the insula and the cingulate (supplementary Figure S3, available at *Annals of Oncology* online) [265]. However, cerebral MRI might also be inconspicuous in allo-HSCT recipients with HSV encephalitis [2, 73].

HSV encephalitis should immediately be treated with aciclovir [AII_t] [73, 185–187].

In rare cases of aciclovir resistance, foscarnet may be administered [CIII] [190]. Patients with HSV encephalitis have a good overall prognosis, but a large proportion of patients (up to 70%) recover with neurological sequelae [2, 187].

cytomegalovirus. CMV CNS disease is typically characterized by ventriculo-encephalitis, retinitis and polyradiculopathy [195, 266, 267]. CSF CMV PCR has a high sensitivity (up to 100%) for the diagnosis of CMV CNS disease [A] [69–72]. Detection of CMV in CSF by viral cultures might only be used as an adjunctive test since it has a low sensitivity of ~20% [C] [69, 72].

CMV CNS disease is commonly treated with ganciclovir or foscarnet [AIII] [188]. Some authors recommend a combination of both agents [BIII] [188, 195–197]. Cidofovir as single agent or in combination with foscarnet or ganciclovir might be used for salvage treatment [CIII] [195, 200, 201]. Some reports support the use of leflunomide to control CMV disease [CIII] [201, 268, 269]. There are no systematic data showing a benefit of the routine administration of CMV hyperimmunoglobulin in patients with hematological disorders and CMV disease.

Epstein-Barr virus. Except for patients with allo-HSCT, EBV disease other than infectious mononucleosis is a rare entity. Diagnosis of EBV meningoencephalitis is based on CSF PCR [A] [2, 73–75]. However, brain-biopsy-proven EBV meningoencephalitis in conjunction with a negative CSF EBV PCR has been reported [76].

A reduction of immunosuppression should be attempted whenever possible in patients with EBV disease or infection [AIII] [188]. The role of rituximab in EBV disease (i.e. presence of EBV organ involvement) remains to be elucidated despite the fact that first experiences suggest that pre-emptive treatment of EBV infections (i.e. EBV reactivation only) might reduce the incidence of post-transplant lymphoproliferative disorder [270]. Likewise, it remains unclear whether antivirals are beneficial in EBV disease [188]. Ganciclovir, valganciclovir or foscarnet might be used to treat EBV meningoencephalitis [BIII] and there are few case reports on the potential efficacy of aciclovir in this situation [CIII] [188, 202–209].

human herpes virus-6. HHV-6 CNS disease (mainly encephalitis) has rarely been described except in allo-HSCT recipients [2, 7, 77, 78, 210]. HHV-6 encephalitis typically

affects allo-HSCT recipients with unrelated (mainly cord blood) donors and it frequently develops at the time of engraftment (or shortly thereafter) [2, 7]. Common clinical symptoms include alteration of consciousness, short-term memory loss and seizures [2, 7, 271]. The diagnostic method of choice for diagnosis of HHV-6 meningoencephalitis is quantitative CSF PCR [A] [77, 78]. However, it should be noted that HHV-6 DNA might be detected in CSF in a significant proportion of asymptomatic allo-HSCT recipients [79]. CSF analysis might show elevated protein levels and, more rarely pleocytosis [2, 77]. Imaging abnormalities which typically involve the temporal lobe are more likely visible in MRI than in CT scan (supplementary Figure S4, available at *Annals of Oncology* online) [2, 77]. Despite this, cerebral MRI might be normal in the early phase of HHV-6 meningoencephalitis in allo-HSCT recipients [2, 77, 78].

Ganciclovir or foscarnet could be used as first-line therapy for HHV-6 meningoencephalitis [AIII] [7, 8, 210–213]. Cidofovir can be administered as second-line treatment [CIII] [215].

varicella zoster virus. Primary VZV infection (chickenpox) occurs rarely in patients with hematological disorders, since VZV-seronegativity in adulthood is rare (~5%). In VZV-seropositive recipients, VZV disease after allo-HSCT most commonly manifests as dermatomal herpes zoster but a VZV meningoencephalitis may occur [2, 216, 217]. Small patient series indicate that CSF PCR has a similar good sensitivity and specificity for diagnosis of VZV meningoencephalitis as for other herpes viruses [A] [80–82]. The CSF VZV viral load determined by PCR might correlate with the severity and the duration of VZV meningoencephalitis [218]. Diagnosis of VZV meningoencephalitis may be confirmed by serological tests such as detection of intrathecal VZV glycoprotein E [272]. Rash and CSF pleocytosis might be absent in patients with cerebral VZV vasculopathy (such as strokes). In this situation, detection of CSF anti-VZV IgG antibodies might have a higher sensitivity than CSF VZV PCR [B] [83].

VZV CNS infections can be successfully treated with aciclovir [AIII] [2, 73, 218]. However, aciclovir resistance could occur and there are case reports on fatal CNS meningoencephalitis in allo-HSCT recipients despite early therapy with high-dose aciclovir [216]. These patients might benefit from a combination of aciclovir and foscarnet [CIII] [219].

JC virus. JC virus-related PML typically affects severely immunocompromised hosts such as Acquired Immune Deficiency Syndrome (AIDS) patients or allo-HSCT recipients [2, 273]. CNS biopsy of suspicious lesions is required for definitive diagnosis of PML [A]. The typical triad (demyelination, bizarre astrocytes and enlarged oligodendroglial nuclei) can frequently be demonstrated by histopathological work-up in biopsies which might be combined with tissue and CSF JC virus (dual qualitative-quantitative nested) PCR [A] [86, 88, 89]. MRI typically shows abnormalities in the posterior white matter without contrast enhancement (supplementary Figure S5, available at *Annals of Oncology* online) [274]. The diagnosis of PML could also be established without CNS biopsy in immunocompromised patients with typical clinical symptoms

and characteristic findings by neuroimaging together with a positive CSF JC virus PCR [A] [86].

Immune reconstitution seems to be crucial for treatment of PML, as suggested by the observation that the incidence of PML could be markedly reduced in AIDS patients by the introduction of highly active antiretroviral therapy (HAART) [273, 275]. However, PML might develop or worsen (in the case of pre-existing PML) at the beginning of HAART (PML-immune reconstitution inflammatory syndrome, IRIS) [273, 275, 276]. PML-IRIS has also been described during withdrawal of agents which are associated with the occurrence of PML, such as natalizumab [277].

Immunosuppressives should be reduced in allo-HSCT recipients with PML whenever possible [AIII] [12]. Treatment with cidofovir may be beneficial in some patients with PML [2, 278, 279]. In contrast, other allo-HSCT recipients as well as a larger series of 370 AIDS patients with PML did not improve after treatment with cidofovir [DII_{tu}] [12, 221]. Several experimental approaches such as adoptive T-cell therapy or administration of interleukin-2, mefloquine or mirtazapine have been tested as a treatment option for PML [12, 278–280]. Since none of them has clearly shown to be effective in larger series of patients they are recommended within experimental protocols only [DIII].

conclusions

Diagnosis of CNS infections remains a great challenge in patients with hematological disorders since symptoms might both be masked and be mimicked by other conditions such as metabolic disturbances or consequences from antineoplastic treatment. Thus, awareness of this complication is crucial and any suspicion of a CNS infection should lead to timely and adequate diagnostics and treatment to improve the outcome in this population.

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