



Review

CNS infections in patients with hematological or oncological diseases (including cellular therapies) – 2024 update of the guideline of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO)

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ABSTRACT

Background: Infections of the central nervous system (CNS) occur in up to 15 % of patients with hematological or oncological diseases (HOD), particularly in high-risk populations. The most common causative agents are viruses or fungi. Prompt initiation of adequate diagnostic procedures and anti-infective treatment is crucial, as treatment delays increase mortality.

Methods: We present an update of our previous guideline published in 2016 on the management of CNS infections in patients with HOD. The grading of recommendation strength and level of evidence followed the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) standards, based on a systematic literature review and a stepwise consensus process involving experts in internal medicine, hematology, oncology, infectious diseases, neurology, microbiology, and radiology. This process included several web-based meetings by the guideline panel, whereas the final recommendations were approved by the assembly of the Infectious Diseases Working Party of the German Society of Hematology and Medical Oncology in September 2024.

Findings and interpretation: Evidence-based recommendations on the diagnosis and treatment of CNS infections in adult patients with HOD are essential in daily clinical practice to improve outcomes for patients at high risk of morbidity and mortality.

What is new?

Since the 2016 AGIHO guideline on CNS infections, several important updates have been introduced. Novel molecular techniques, including next-generation sequencing (NGS) and digital droplet PCR (ddPCR), are now established as additional diagnostic tools. Chromosomally integrated HHV-6 (ciHHV-6) is recognized as a distinct clinical entity that requires specific diagnostic confirmation but does not warrant antiviral therapy. Recommendations on corticosteroid use have been refined in a pathogen-specific manner, with early administration advised in suspected bacterial meningitis and discontinuation once a viral etiology is established.

Treatment options for viral CNS infections have expanded, particularly for EBV encephalitis and progressive multifocal leukoencephalopathy (PML). The fungal section now provides structured management strategies for mucormycosis, guidance for rare molds, and recommendations for ophthalmological assessment in cases of *Candida* infection. For bacterial disease, emphasis is placed on antibiotic initiation within one hour of hospital admission and on using the CHANCE score to support differential diagnosis. Finally, MRI interpretation is enhanced by defined imaging features and risk stratification estimates.

1. Introduction

Infections of the central nervous system (CNS) are associated with high morbidity and mortality. The outcome largely depends on rapid diagnosis and appropriate treatment. Immunocompromised patients are at increased risk for CNS infections, which may present atypically in this population and can be caused by uncommon or opportunistic pathogens [1–3]. Furthermore, non-infectious conditions, e.g., CNS manifestations of the underlying malignancy, might mimic CNS infections in immunocompromised patients [4,5].

A standardized case definition for different types of presumed CNS infection (e.g., encephalitis, encephalopathy, myelitis) is important for epidemiological surveillance, clinical research, and outbreak investigations [6,7]. As has been defined for various infections [8,9], *confirmed (proven)* or *probable* should be distinguished from *possible* CNS infection [6,10,11]. However, it should be noted that definitions for the

likelihood of CNS infections are available only for selected pathogens such as cytomegalovirus (CMV) [12], JC virus (JCV)-induced progressive multifocal leukoencephalopathy (PML) [13], different invasive fungal diseases (IFD) [8], and a few others [10]. In addition, these definitions are not always standardized, are not widely known, are only partly applicable in clinical practice, and do not include novel techniques such as cerebrospinal fluid (CSF) next-generation sequencing (NGS) [14].

CNS infections frequently represent a diagnostic and therapeutic challenge, particularly in severely immunocompromised patients. In 2016, comprehensive guidelines on the diagnosis and treatment of CNS infections in patients with hematological or oncological diseases (HOD) were published by the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO) [2]. Here, we present an update of these guidelines.

2. Methods/consensus process

This guideline focuses on the characteristics (e.g., epidemiology, pathogenesis), the diagnostics and the treatment of adult patients with HOD, including patients after autologous (auto) or allogeneic (allo) hematopoietic cell transplantation (HCT) or chimeric antigen receptor (CAR) T-cell therapy. Consistent with other AGIHO guidelines, definition and classification of strength of a recommendation (SoR), and level (“quality”) of evidence (LoE) were based on European Society of Clinical Microbiology and Infectious Diseases (ESCMID) criteria (Table 1) [15]. Further details of the consensus process are shown in the [Supplementary Material](#).

3. Epidemiology and causative pathogens

Larger, comprehensive, prospective data using standardized case definitions on the incidence of CNS infections in patients with HOD are lacking. Patients who underwent allo-HCT are commonly severely immunocompromised and belong to the population with the highest risk of CNS infections, particularly if further potential risk factors are present, such as the presence of graft-vs.-host disease (GvHD) or the use of T-cell depletion [3].

A prospective study conducted by the European Society for Blood and Marrow Transplantation (EBMT) group between the years 2000 and 2002 estimated the frequency of CNS infections at 0.1 % after auto-HCT and at 2.6 % after allo-HCT [1]. The cumulative incidence of CNS infections was 4.1 % at 1 year and 5.5 % at 5 years in a retrospective analysis of 353 consecutive allo-HCT recipients [16]. A different monocentric retrospective comprising 888 patients found around 1 % CNS infections but established CNS infection as a major determinant of adverse non-relapse mortality [17]. Epidemiological data are even fewer in patients with HOD not undergoing HCT [18,19].

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Table 1
Strength of recommendation (SoR) and level (“quality”) of evidence (LoE) [15].

Grade (SoR)	A: AGIHO ‘strongly’ supports a recommendation for use B: AGIHO ‘moderately’ supports a recommendation for use C: AGIHO ‘marginally’ supports a recommendation for use D: AGIHO supports a recommendation ‘against’ use
Level (“quality”) (LoE)	I: Evidence from ≥ 1 properly designed RCT II*: Evidence from ≥ 1 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 RCTs t: Transferred evidence, that is, results from different patients’ cohorts, or similar immune status 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

Note. AGIHO, Infectious Diseases Working Party of the German Society of Hematology and Medical Oncology; RCT, randomized controlled trial.

The spectrum of pathogens differs between immunocompromised and immunocompetent patients. In contrast to the general population, where bacteria and herpes simplex virus (HSV) are the most frequently detected causes of CNS infection [7], fungi predominated in the above-mentioned EBMT study, followed by viruses and *Toxoplasma* spp. [1]. CNS infections by different fungi, including *Aspergillus* spp., *Cryptococcus neoformans*, and *Candida* spp., occurring particularly in patients with prolonged neutropenia or advanced immunosuppression, were described [20].

Human herpes virus-6 (HHV-6) was most frequently detected in a study recruiting HCT recipients more recently [16]. However, CMV, Epstein-Barr virus (EBV), and the JCV-associated PML might also affect patients with advanced immunosuppression [21]. PML has mainly been described in patients with acquired immune deficiency syndrome (AIDS), but it may also occur in the context of HCT or during treatment with different drugs, including rituximab [22,23].

Listeria meningitis was the most frequent bacterial meningitis (29 %) in a prospective observational cohort study comparing patients with HOD and those without HOD [19]. It was also more common in patients with HOD than without HOD (8 %). In contrast, meningococcal meningitis was much less frequent in patients with HOD than in patients without HOD. A preponderance of *Listeria* meningitis in patients with HOD/who are immunocompromised vs. patients without HOD/without immunocompromised state has also been observed [24,25].

However, rare pathogens such as *Curvularia* spp., *Histoplasma capsulatum*, *Mycobacterium houstonense*, adenovirus, enterovirus, and infections by West Nile virus (WNV) or tick-borne encephalitis among others might occur [26–28]. Some of these pathogens may not be detected by classical microbiological methods but only by CSF NGS [29].

4. Pathogenesis

See [Supplementary Material](#).

5. Prophylaxis

See [Supplementary Material](#).

6. General strategies to manage CNS infections in patients with HOD

6.1. General considerations

Some principal aspects regarding the management of CNS infections

in patients with HOD should be kept in mind [2]:

(I) A high level of awareness is required – particularly in severely immunocompromised patients, such as those after allo-HCT – as neurological symptoms are nonspecific *per se* and can be caused either by non-infectious CNS disorders such as metabolic encephalopathy, drug-induced disorders, vascular events (e.g., bleeding, strokes), immune-related disorders (e.g., CNS GvHD), or relapse of the underlying malignancy. In the monocenter analysis mentioned, the cumulative incidence of major neurological complications was close to 15 %, with the minority being infectious in origin [17]. The typical clinical signs of meningitis (triad of fever, nuchal rigidity, and mental status changes) were observed in 5 % of patients with HOD who had a positive CSF bacterial or fungal culture [18].

(II) The pattern of immunosuppression (e.g., defects in cell-mediated immunity vs. defective humoral immunity) might predispose patients to distinct types of infections, including those involving the CNS [3]. Bacterial, fungal, and viral CNS infections typically occur in neutropenic patients. Defects in T-cell immunity or in macrophage function predispose for cerebral toxoplasmosis and cryptococcal meningitis [4,30]. Furthermore, the typical onset of CNS infections after allo-HCT depends on the pathogen type, with HHV-6 infections usually occurring early and PML rather late after transplantation [1,3].

(III) Diagnostic findings (e.g., neutrophilic CSF pleocytosis) might differ between immunocompromised and non-immunocompromised patients. In the above-mentioned retrospective study comprising patients with HOD with positive CSF bacterial or fungal culture [18], only 75 % of patients demonstrated CSF pleocytosis, while the median CSF white blood cell (WBC) count was only 74 cells/mm³. Notably, 4 of 6 neutropenic patients had 0–1 CSF WBC/mm³ and 2 had normal CSF [18]. However, CSF pleocytosis remains an important criterion for the diagnosis of infectious encephalitis [31].

(IV) Diagnostic findings should always be interpreted in the clinical context, primarily in combination with other methods such as CSF analysis and neuroimaging. For example, CSF EBV polymerase chain reaction (PCR) might often be negative in children with acute EBV infectious encephalitis but might also be non-specific or be associated with CNS lymphoma if positive, especially in adults [7].

(V) The frequency of some CNS infection-causing pathogens (e.g., *Histoplasma capsulatum*, *M. tuberculosis*, WNV) in immunocompromised patients may vary substantially between different geographic regions [32,33].

6.2. Diagnosis

Timely initiation of adequate diagnostics such as neuroimaging, CSF sampling, and/or CNS biopsy in selected cases is crucial in patients with HOD with neurological symptoms (Figure 1) [1]. Neuroimaging is typically based on contrast-enhanced magnetic resonance imaging (MRI) of the neurocranium but may also include the spinal cord. Whenever possible, MRI should be performed prior to lumbar puncture for CSF sampling, as an intervention-induced non-infectious thickening of the meninges may mimic infectious meningitis. If there are focal neurological signs or signs of increased intracranial pressure, imaging is mandatory prior to lumbar puncture, which may even be contraindicated in such cases depending on imaging results. Computed tomography (CT) scan of the skull might be done in emergency situations (e.g., to exclude cerebral bleeding, infarction, or ischemia) or to detect bone-erosion. However, at least if the origin of the neurological symptoms remains still unclear, MRI should routinely be added [34,35]. In patients with acute leukemia, a combination of clinical/laboratory and MRI findings can help to distinguish between CNS infection or CNS involvement of the underlying disease (fever, altered consciousness, co-infection, and parenchymal MRI lesions [for infection] vs. hyperleukocytosis, and no complete remission [for underlying disease] as independent predictors) [36]. Metabolic imaging, e.g., by ¹⁸F fluorodeoxyglucose positron emission tomography CT scan, may help to

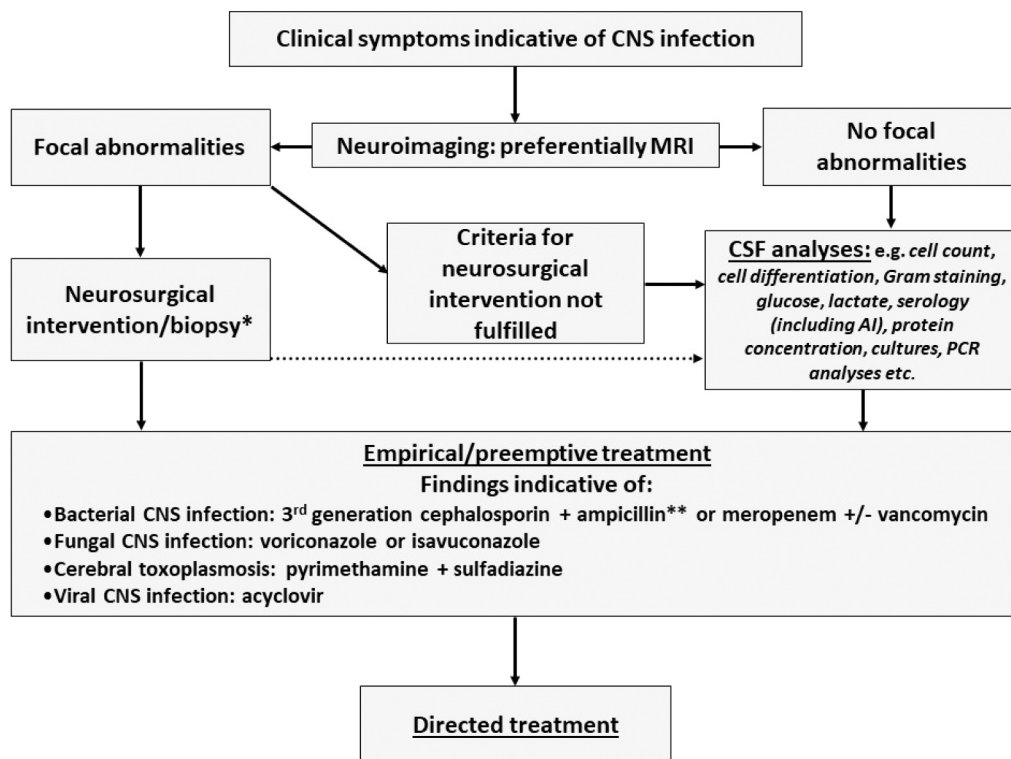


Fig. 1. Algorithm to diagnose and to treat CNS infections in patients with HOD. Clinical symptoms indicative for CNS infections may include focal (e.g., paresis, numbness, focal seizure) and non-focal (e.g., headache, fever, consciousness disturbances) abnormalities. *The decision on brain biopsy/neurosurgical resection should always be made based on technical feasibility, the suspected causative pathogen, and other factors (e.g., presence of thrombocytopenia). Brain biopsy might not be required to establish the diagnosis of PML or CNS toxoplasmosis in patients with typical neuroimaging findings and positive CSF PCR. **Ampicillin should commonly be used in adequate dosages, e.g., 150–200 mg/kg BW/day intravenously in equally divided doses every 3–4 h, or 12.000 mg/day intravenously in divided doses every 4 h. **Note.** AI, antibody index; CNS, central nervous system; CSF, cerebral spinal fluid; HOD, hematological or oncological diseases; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PML, progressive multifocal leukoencephalopathy.

establish the diagnosis of a CNS infection under certain circumstances [5].

CSF sampling and analyses, routinely performed after exclusion of increased intracranial pressure by neuroimaging, should include various diagnostic methods such as different staining and microscopy techniques, culturing, serological assays, PCR assays, and more recently, NGS approaches [29,37,38]. In all CSF examinations of bacterial and viral origins, antibody index (AI) should routinely be used to confirm CNS infection; the AI may become positive only over time but can be of great help in difficult differential diagnoses. Typically, neuroimaging and CSF analyses are sufficient to diagnose meningitis, encephalitis, or meningoencephalitis – typically caused by viruses, bacteria, or more rarely fungi such as *Cryptococcus* spp. or *Aspergillus* spp. However, biopsy of focal CNS lesions might be necessary in selected cases such as PML [13] or cerebral abscesses, e.g., caused by *Nocardia* spp. [39]. Focal lesions, for example, caused by *Aspergillus* spp., *Mucorales*, or *Toxoplasma* spp. are frequently diagnosed by cerebral biopsy or neurosurgical intervention [39,40].

6.3. Treatment

Parallel to neuroimaging and the collection of CSF and blood cultures, empirical anti-infective treatment should be initiated immediately in all patients with suspected CNS infection, as treatment delay may increase mortality (A-II_{t,u}) (Figure 1) [41,42]. Adjunctive dexamethasone in addition to antibiotics reduces mortality and sequelae in patients with *Streptococcus pneumoniae* meningitis and hearing loss in those with *Haemophilus influenzae* type b meningitis [43]. Therefore, initiating dexamethasone concomitantly with the first dose of antibiotics and as soon as possible if bacterial meningitis is suspected is recommended by

international guidelines [44,45]. After isolation and *in vitro* susceptibility testing of a (potentially) causative pathogen, antimicrobial treatment should be modified accordingly [2].

Therapeutic drug monitoring (TDM) might be useful for selected antimicrobial agents, such as 5-fluorocytosine (5-FC), voriconazole, or posaconazole, with the aim to ensure efficacy and minimize toxicity (B-II_u) [46]. This is particularly relevant in patients with HOD who have impaired gastrointestinal resorption and/or certain co-medications causing substantial interactions, such as calcineurin inhibitors or kinase inhibitors. Adjunctive treatment may include neurosurgery, platelet transfusion, and the administration of dexamethasone, anti-convulsants, sedatives, or antipyretics, depending on the specific clinical situation of the patient.

7. Distinct causative pathogens

7.1. Viruses

In everyday clinical practice, some patients with viral meningitis receive dexamethasone until bacterial meningitis has been ruled out. This approach aligns with international guidelines, as early corticosteroid administration is beneficial, particularly in pneumococcal meningitis. Recent data demonstrate that there is no dose-dependent relationship between dexamethasone and an unfavorable outcome in patients diagnosed with viral meningitis. However, once a bacterial cause has been ruled out, dexamethasone should be discontinued, as adjunctive corticosteroid therapy is not generally indicated in viral meningitis [47,48]. Details for adjunctive corticosteroid therapy are specified below for different causative agents.

7.1.1. CMV

CMV-caused CNS infections may typically occur as encephalitis, meningoencephalitis, ventriculitis, or retinitis [49]. Even though these infections are rare even in patients after allo-HCT, they may also occur under letermovir prophylaxis due to low CNS penetration of the compound [50]. Diagnosis of CMV encephalitis or meningoencephalitis is typically based on CSF PCR in patients with non-specific neurological symptoms (A-II_u) (Table 2) [27,51,52]. Requiring CMV detection in the CNS tissue to diagnose *proven* CMV encephalitis or ventriculitis [53] is supported by little data that correlate CNS tissue biopsy or autopsy-proven CNS CMV infection and CSF PCR [52]. However, CNS tissue biopsy is rarely performed in patients with suspected CNS CMV infection in clinical routine. MRI of the neurocranium shows typical CMV abnormalities only in one-third of patients with CMV meningoencephalitis (A-II_{t,u}) [27]. *Proven* CMV retinitis is defined by some authors by a typical pattern in ophthalmological examination (A-II_{t,u}) [53,54], while other definitions additionally include positivity for CMV DNA in the vitreous fluid besides negativity for DNA of HSV and varicella-zoster virus (VZV) (A-II_u) (Table 2) [55].

CMV encephalitis is typically treated with ganciclovir (A-III) [56]. Alternatively, foscarnet as a single agent or in combination with ganciclovir can be used (B-III) [56]. Cidofovir is restricted to selected cases, mainly due to considerable side effects such as nephrotoxicity (C-III) (Table 3) [2,57]. In refractory cases, antiviral CMV treatment might be adjusted after viral genotyping to exclude resistance mutations [58]. Other treatment options such as intravenous (B-III) or intrathecal (C-III) CMV-specific cytotoxic T-cells (CTLs) have been effective in a few patients [59]. Animal studies and first clinical experiences suggest that maribavir shows poor CNS penetration [60]. Immunoglobulins – mainly given intravenously [IVIG] but also intrathecally – might also be used,

albeit a definitive proof of their efficacy is lacking [61].

CMV retinitis should be treated with systemic and intravitreal ganciclovir (A-I) (Table 3) [62–64]. Antiviral intravitreal treatment alone (i.e., without concomitant systemic treatment) is usually not recommended, also because the contralateral eye might be affected in a significant proportion of patients [65]. Other treatment options for CMV retinitis include systemic antiviral treatment alone (e.g., ganciclovir or foscarnet) (B-II_{t,u}) [66], intravitreal foscarnet injections in combination with systemic antiviral treatment (B-II_{t,u}) [65–68], or infusion of CMV-CTLs (C-III) [64]. Limited data suggest that letermovir may also be used as salvage treatment for CMV retinitis [69].

7.1.2. EBV

MRI should be the imaging procedure of choice for suspected EBV encephalitis (A-II_{t,u}) (Table 2) [70,71]. Using MRI, EBV encephalitis-related abnormalities can be found in about two-thirds of cases. If both CT and MRI are performed, approximately 50 % show consistent findings for both types of imaging can be found, whereas in about 50 % of the cases, a normal CT is seen but an abnormal MRI [71]. In EBV encephalitis, MRI typically shows multifocal areas of high signal intensity on T2-weighted fluid-attenuated inversion recovery (FLAIR) images in the deep gray nuclei and subcortical white matter [70]. Most often, the supratentorial brain, although the cerebellum, brainstem, myelon, and optic nerve are the involved sites [70,71].

Testing for EBV in CSF of adults is not routinely recommended unless the patients are severely immunocompromised (A-III) [21]. Leukopenia, thrombocytopenia, and/or elevated transaminases are suggestive of EBV as the causative pathogen in patients with clinical signs of encephalitis/meningoencephalitis and acute (primary) EBV infection (infectious mononucleosis) (A-III) [7]. PCR in CSF is the preferred method for the

Table 2
Diagnosis of selected viral CNS infections in patients with HOD.

Virus	Intention	Intervention	SoR/LoE	References	Comments
CMV	To diagnose CMV encephalitis	MRI	A-II _{t,u}	[27]	Typical abnormalities in about 1/3 of patients Few data compared to brain biopsy [52]
		CSF CMV PCR	A-II _u	[27,51,52,56,140,239,240]	
		CSF CMV NGS	B-III	[73,123,141,142,241]	Might be false positive and false negative (compared to PCR)
	To detect CMV resistance mutations	CSF CMV PCR	C-III (primary), A-III (refractory)	[58]	Intrahost diversity of CMV resistance might be observed
	To diagnose CMV retinitis	Ophthalmological screening	A-II _{t,u}	[53,54,242]	According [53]; sufficient for <i>proven</i> CMV retinitis if an experienced ophthalmologist is available
EBV	To diagnose CMV retinitis	Vitreous fluid CMV PCR	A-II _u	[239]	Might occur under letermovir prophylaxis [50]
	To diagnose EBV encephalitis	MRI	A-II _{t,u}	[70,71]	Abnormalities in about two third of cases [71]
		CSF EBV PCR	B-II _{t,u}	[51,71]	Positive PCR can be non-specific, limited data on significance of EBV in CSF and association with encephalitis
		EBV PCR + serology in blood + EBV CSF PCR	B-II _{t,u}	[11,51,71]	To distinguish primary EBV encephalitis from EBV-associated lymphoproliferative disease
		CSF NGS	B-III	[73,74,123]	Less sensitive than RT-PCR/PCR
HHV-6	To diagnose HHV-6 CNS infection (e.g., encephalitis/myelitis)	MRI	A-II _u	[87,91]	Should be aimed in all patients with suspicion for viral CNS infection
		CSF PCR	A-II _u	[93,94]	ciHHV-6 should be excluded
		CSF NGS	B-III	[29,96]	
HSV	To diagnose HSV encephalitis	MRI	A-II _{t,u}	[102,103]	Abnormalities in 80–100 %
		CSF PCR	A-II _{t,u}	[27,104]	
		CSF NGS	B-III	[105,106]	
JCV (PML)	To diagnose PML	MRI	A-II _{t,u}	[116–118,243]	Typically, T2 hyperintense lesions located in the juxtacortical and deep white matter
		CSF JCV PCR	A-II _u	[119,140,244,245]	
		CSF mNGS	B-III	[123]	
VZV	To diagnose VZV encephalitis	MRI	A-II _{t,u}	[132]	Should be aimed in all patients with suspicion for viral CNS infection
		CSF PCR	A-II _{t,u}	[27,132]	
		CSF mNGS	B-II _{t,u}	[29]	

Note. CMV, cytomegalovirus; CNS, central nervous system; CSF, cerebral spinal fluid; EBV, Epstein-Barr virus; HHV-6, human herpes virus-6; HOD, hematological or oncological diseases; HSV, herpes simplex virus; JCV, JC virus; LoE, level of evidence; MRI, magnetic resonance imaging; (m)NGS, (metagenomic) next-generation sequencing; PML, progressive multifocal leukoencephalopathy; (RT-) PCR, (real-time) polymerase chain reaction; SoR, strength of recommendation; VZV, varicella zoster virus.

Table 3

Treatment options for selected viral CNS infections in patients with HOD.

Virus type	Intention	Intervention	SoR/LoE	References	Comments
CMV	To treat CMV encephalitis	Ganciclovir	A-III	[56]	Consider main side effects (myelotoxicity, nephrotoxicity etc.) and the presence of CMV resistance mutations (e.g., UL97, UL54)
		Foscarnet + /- ganciclovir	B-III	[56]	
	To treat CMV retinitis	Cidofovir	C-III	[57,246]	Few data Poor CNS penetration
		Maribavir	D-III	[60]	
EBV	To treat EBV encephalitis	Intravitreal + systemic ganciclovir	A-I	[63,64,247]	Might be used systemically and intravitreally Might be combined with other antiviral agents and given intravitreally Efficacy as salvage treatment reported Consider combination Indicated by ongoing cyclic lytic infection (significant number of EBV copies in CSF); early treatment may be initiated where suspicion is high based on clinical findings; consider combination with steroids/IVIG
		Foscarnet	B-II _{t,u}	[66,68,248]	
		Cidofovir	B-II _{t,u}	[57,249,250]	
		Letermovir	C-III	[69]	
HHV-6	To treat HHV-6 encephalitis	Rituximab i.v.	B-II _{t,u}	[51,71]	
		Acyclovir, (val)	C-III	[51,71]	
		ganciclovir			
HSV	To treat HSV encephalitis	Ganciclovir	A-II _u	[84,85]	e.g., if acyclovir resistance mutations are suspected
		Foscarnet	A-II _u	[84,85]	
		Ganciclovir	C-II _u	[84,85]	
		+ foscarnet			
JCV (PML)	To treat JCV encephalitis	Acyclovir	A-II _{t,u}	[101,109,110]	
		Foscarnet	B-III	[112]	
		High-dose acyclovir + foscarnet	C-III	[112]	
		Adjuvant steroids	C-II _{t,u}	[113,114]	
VZV	To treat VZV encephalitis	Allogeneic virus-specific T cells	B-II _{t,u}	[125,251–253]	e.g., pembrolizumab, nivolumab
		Immune checkpoint inhibitors	B-II _{t,u}	[125,127,245, 252,254]	
		Acyclovir	A-II _{t,u}	[132,133]	Might be used for acyclovir-resistant cases
		Foscarnet	B-III	[137,138]	

Note. CMV, cytomegalovirus; CNS, central nervous system; EBV, Epstein-Barr virus; CSF, cerebral spinal fluid; HHV-6, human herpes virus-6; HOD, hematological or oncological diseases; HSV, herpes simplex virus; i.v., intravenous; IVIG, intravenous immunoglobulins; JCV, JC virus; LoE, level of evidence; PML, progressive multifocal leukoencephalopathy; SoR, strength of recommendation; VZV, varicella zoster virus

diagnosis of EBV encephalitis (B-II_{t,u}) [51,71]. However, positive EBV PCR in CSF can be non-specific – since positive patients can have diverse clinical aspects, and more than half of these patients have another discernible etiology [72] –, in particular if CSF pleocytosis is not evident and if CSF EBV copy number is low and lower than in blood, and should be interpreted with caution. Therefore, a comprehensive workup is needed to identify other etiologies before considering EBV as the causative pathogen [72]. In cases of suspected EBV encephalitis, additional EBV serology from blood is helpful to distinguish possible from unlikely EBV encephalitis [71]. CSF EBV PCR might be false-negative but also positive without clear evidence of active EBV encephalitis [71]. Therefore, to diagnose EBV encephalitis, EBV PCR in CSF and blood as well as EBV serology (EBV capsid antigen IgG and IgM [VCA] and EBV nuclear antigen IgG [EBNA]) in blood should be considered (B-II_{t,u}) [11,51,71]. Metagenomic NGS (mNGS) is a new tool for detecting pathogens but might be less sensitive than real-time (RT)-PCR/PCR for detecting EBV in CSF (B-III) [73,74]. The presence of EBV CNS infection is further supported by a CSF/serum AI > 1.5 [75].

So far, no specific treatment options for EBV infections have been established and recommendations are mostly based on case series only (Table 3). Corticosteroids, alone or in combination, are often used for treatment of EBV-associated CNS infections (B-II_{t,u}) [71], but potential risks must be weighed against limited benefits [76]. Since B-cells are the primary compartment for EBV [77], consideration can be given to B-cell directed anti-CD20 antibodies such as rituximab for treatment of EBV infections. However, rituximab is rarely used for treatment of EBV encephalitis but should be taken into account whenever possible (B-II_{t,u}) [51,71]. This approach is well known for preventive, preemptive, or therapeutic use for post-transplant lymphoproliferative disorders after allo-HCT but might be associated with substantial morbidity and mortality [78]. Intrathecal rituximab can be considered in selected cases (C-III) [79]. Acyclovir is the most frequently used treatment option for

(primary) EBV encephalitis [71]. However, antiviral agents are indicated only in the ongoing cyclic lytic EBV infection which is demonstrated by a significant number of EBV DNA copies in the CSF. Furthermore, early antiviral treatment may be initiated where suspicion is high based on clinical findings (C-III) [51,71]. Duration of antiviral therapy is not well defined, but 14–21 days should be considered (B-III) [80]. Antivirals can be combined with corticosteroids and/or IVIG, especially for more severe/complicated cases (B-II_{t,u}) [71]. In patients with EBV encephalitis after allo-HCT, rituximab (B-II_u) or combination of antivirals + rituximab (C-II_u) could be an option [51], though there are no trials for proof of concept, thus being an individual treatment regime, no general recommendation can be given. The adoptive transfer of EBV-CTLs to rapidly restore antiviral immunity, especially in allo-HCT patients and/or in patients with refractory infection, could be a further treatment option (B-III) [81]. Data on the use of IVIG for the treatment of EBV encephalitis are scarce, so no clear recommendation can be given.

7.1.3. HHV-6

HHV-6 also belongs to the *Herpesviridae* family and is categorized into two distinct subtypes, HHV-6A and HHV-6B, which have different pathogenic properties and are associated with different diseases [82]. Primary infection is typically asymptomatic or manifests as a transient, nonspecific febrile illness, accompanied by an exanthema subitum. Primary infection results in persistent latent infection, possibly leading to viral reactivation during immunosuppression [83]. HHV-6B, rather than HHV-6A, is a leading cause of encephalitis in allo-HCT recipients, with high morbidity and mortality [51,84]. The risk of developing HHV-6 encephalitis is significantly higher in umbilical cord blood (cb) HCT than in allo-HCT. The incidence is reported to vary from 5 % to 21 % [85–87]. Chromosomally integrated HHV-6 (ciHHV-6) represents a relevant clinical entity, occurring in approximately 0.2–1 % of

individuals and leading to persistently high levels of viral DNA in cellular samples, including whole blood and tissue biopsies [88]. The HHV-6 genome is susceptible to integration into the human genome. If HHV-6 encephalitis is suspected, ciHHV-6 testing, preferably using hair or nail samples, should therefore be performed to confirm chromosomal integration. Detection of ciHHV-6 alone does not indicate active infection, and antiviral therapy is not recommended in these cases. In patients with neurological symptoms and confirmed ciHHV-6, alternative infectious etiologies should be carefully investigated. Therapeutic intervention applies only in cases of true HHV-6 reactivation, which should be differentiated from ciHHV-6 by integrating clinical presentation with diagnostic markers, such as serial HHV-6 DNA kinetics, a disproportionately higher HHV-6 DNA load in CSF compared to blood, compatible MRI findings, and the presence of CSF pleocytosis [89,90].

MRI may show hyperintense lesions on T2-weighted FLAIR imaging of the bilateral hippocampus and amygdala (A-II_u). Only 60 % of patients with HHV-6B encephalitis present limbic encephalitis findings on MRI in a retrospective study. The basal ganglia and various regions of the cortex may show abnormal findings [85,87,91,92]. These findings are more frequently identified with MRI than with CT scans. During the initial stages of HHV-6 meningoencephalitis in allo-HCT recipients, MRI may not detect any abnormalities [85].

PCR is the primary method for diagnosing HHV-6, and a range of RT-PCR assays are available for quantifying HHV-6 DNA load. However, there is no consensus on differentiating between HHV-6A and HHV-6B, and there is considerable variation in reported HHV-6 DNA levels between laboratories (A-II_u) [93,94]. If HHV-6A is detected after HCT, ciHHV-6 should always be considered, as HHV-6A reactivation is atypical but is responsible for up to one-third of ciHHV-6 cases [95]. Diagnosing HHV-6B encephalitis after transplantation by mNGS has been rarely described (B-III) (Table 2) [29,96].

Intravenous foscarnet or ganciclovir is recommended to treat HHV-6B encephalitis, with the choice of drug depending on the side-effect profile and patient comorbidities. Dosages are 2x 90 mg/kg or 3x 60 mg/kg BW for foscarnet or 2x5 mg/kg BW for ganciclovir, respectively (A-II_u) (Table 3) [84,85]. Antiviral therapy should be continued for at least three weeks and until HHV-6 DNA is cleared from blood and from CSF [86]. In severe cases, combination therapy with foscarnet 60 mg/kg BW (depending on renal function) three times daily at 8-hour intervals plus ganciclovir 5 mg/kg BW twice daily at 12-hour intervals may be worth considering (C-II_u) [84,97]. The use of cidofovir might be limited, as *in vitro* evidence suggests its limited penetration into the CNS [85,86]. No effective preventive or prophylactic strategies have been identified. In particular, the prophylactic use of foscarnet did not show a significant reduction in the incidence of encephalitis (D-II_h) [98]. Adoptive immunotherapy with HHV-6-CTLs represents a therapeutic approach for HHV-6. Preliminary uncontrolled studies indicate that this treatment is safe and potentially efficacious (B-II_{t,u}) [99].

7.1.4. HSV

Herpes simplex encephalitis (HSE) is the most frequent cause of sporadic infectious encephalitis worldwide [100]. HSV-1 infection is common, affecting 60–90 % of older adults worldwide. While HSV-2 can also cause encephalitis (particularly in immunocompromised individuals), HSV-1 is the main cause of HSE in adults and children. The global incidence of HSE is estimated at 2–4 cases per 100,000 [34]. The nonspecific signs and symptoms of viral encephalitis combined with its rapid progression, make it sometimes difficult to diagnose and treat in a timely manner. Diagnostic strategies for HSE include laboratory testing and neuroimaging, preferably with MRI [100,101].

MRI is the preferred imaging modality to identify characteristic abnormalities associated with HSE. Temporal lobe abnormalities, such as edema, hemorrhage, or necrosis, are indicative of HSE. MRI offers greater sensitivity than CT [102]. Although less sensitive, CT may be performed initially to assess gross structural abnormalities and to rule out other causes of neurological symptoms (A-II_{t,u}) (Table 2) [102,103].

CSF PCR analysis is the gold standard diagnostic test for HSE, demonstrating high sensitivity and specificity. Positive PCR results confirm the presence of HSV DNA in the CNS (A-II_{t,u}) (Table 2) [27,104]. In the diagnosis of HSE, mNGS is becoming increasingly used. However, in clinical practice, a large number of HSE patients with normal CSF have been diagnosed by mNGS (B-III) (Table 2) [105,106]. Very early on, the PCR may not yield positive results. Thus, given the presence of a clinical suspicion, initiation of antiviral treatment is obligatory – never wait for results of the PCR [34,107]. The AI is typically positive (e.g., >1.5) [75] in the course of HSE, in the majority of cases during the 2nd and 3rd week after symptom onset [34].

In some cases, additional tests such as an electroencephalogram may be used to assess brain function and detect abnormal electrical activity (B-II_{t,u}) [108].

Intravenous acyclovir is the drug of choice for treating HSE. The dose should be adjusted according to renal function. The duration of antiviral treatment is not well defined, ranging from 14 to 21 days, although longer courses may be in severe cases or in patients with HOD (A-II_{t,u}) (Table 3) [101,109,110]. The incidence of acyclovir-resistant HSV has been reported to be approximately 0.5 % and 3.5–10 % in immunocompetent and immunocompromised patients, respectively [111]. In the case of clinical resistance and failure to respond to antiviral therapy at an appropriate dose, resistance testing should be performed. In rare cases of acyclovir resistance (clinically or *in vitro*-proven), foscarnet can be used as single agent (B-III) or in combination (C-III) [112]. Adjunctive use of corticosteroids may be considered to reduce inflammation and mitigate immune-mediated damage in HSE. However, the benefit for survival is still not proven (C-II_{t,u}) (Table 3) [113,114].

7.1.5. JCV

PML, which is typically caused by the JCV, is a frequently fatal disease. Rarely, the BK virus has been isolated from CSF in patients with PML or encephalitis [115]. Most often, PML occurs in allo-HCT recipients or in patients receiving B-cell-depleting agents such as rituximab or obinutuzumab [22].

Proven diagnosis of PML is based on the histopathological triad (demyelination, bizarre astrocytes, and enlarged oligodendroglial nuclei) with detection of JCV protein and/or JCV DNA or the detection of JCV DNA in the CSF in combination with both imaging and clinical features [13].

MRI of the neurocranium should be performed in all patients with suspected PML (A-II_{t,u}) (Table 2) [116], while imaging patterns might differ between rituximab- and natalizumab-associated PML [116]. Special imaging approaches for MRI-based discrimination of PML variants are still experimental (C-III) [117].

However, in clinical routine, diagnosis is largely based on the detection of JCV in the CSF by PCR in combination with a typical appearance in MRI and clinical features (A-II_u) (Table 2) [118]. A study including 62 CSF samples from 31 PML patients showed a strong correlation between digital droplet PCR (ddPCR) assay and the gold standard of RT-PCR, whereas the sensitivity of the ddPCR assay was increased (B-II_{t,u}) [119]. Despite this, CSF JCV might also be negative in PML. In these rare cases, a *definitive* diagnosis can be established only by brain biopsy [120,121]. CSF or tissue NGS might additionally be used, albeit the data are limited (B-III) (Table 2) [122,123]. A study including 11 HIV patients with PML found a 93 % sensitivity and a 100 % specificity for CSF mNGS [123].

Treatment options for PML are limited. Reduction of immunosuppression should always be considered for (B-III). However, there are no systematic data on this approach, and it might not always be possible [2,124]. In a systematic review, 13 of 29 patients (45 %) with PML who underwent allo-CTL treatment improved (B-II_{t,u}) (Table 3) [125]. Since T-cell exhaustion might be involved in the pathogenesis of PML, immune checkpoint inhibitors (ICI; e.g., pembrolizumab, nivolumab) may also restore T-cell function. The same working group reported on 30 PML patients – including 17 patients with lymphoproliferative diseases –

treated with ICI and improving in 11 patients (37 %) (**B-II_{t,u}**) (Table 3) [125]. Other agents such as mirtazapine, mefloquine, or IVIG have been evaluated for PML treatment [126,127]. However, there are no larger systematic data supporting their use (**C-III**). A pooled analysis from one prospective and five cohort studies in patients with AIDS and PML found that cidofovir has no significant impact on this disease (**D-II_{t,u}**) [128]. PML-immune reconstitution inflammatory syndrome (IRIS) – a paradoxical worsening of PML symptoms with immunoreconstitution – has mainly been reported in AIDS patients undergoing antiretroviral therapy [129] or in natalizumab-treated multiple sclerosis [130], but might also occur after ICI treatment [125,127].

7.1.6. VZV

Neurological complications of VZV occur after primary infection or after reactivation of latent infection. Vascular damage may be associated with encephalitis, including ventriculitis, large vessel vasculitis complicated by ischemic stroke, small vessel vasculitis with demyelinating lesions [89]. Myelitis is another CNS manifestation of VZV [131].

VZV can also cause sporadic cases of viral encephalitis in the Western world. Mortality rates of sporadic VZV encephalitis range between 9 % and 20 % [101,132].

The initial infection with VZV manifests as varicella (chickenpox), followed by a period of viral latency in sensory neurons in the brain or dorsal root ganglia [132]. Reactivation of VZV can lead to a variety of clinical outcomes, with herpes zoster (shingles) being the most common [132]. In rare cases, VZV reactivation can result in severe neurological complications, including encephalitis, cerebellitis, meningitis, or CNS vasculitis [132,133]. Common symptoms of varicella encephalitis include headache, altered mental status, and focal neurological deficits [47]. MRI may show encephalitic changes, but these findings are often non-specific and may also appear normal (**A-II_{t,u}**) [132].

PCR analysis of VZV DNA is the preferred diagnostic method to detect VZV in CSF (**A-II_{t,u}**) (Table 2) [27,132]. In addition, particularly in late-stage infection or VZV vasculitis, where PCR results may be negative, monitoring intrathecal anti-VZV IgG levels in CSF may also be informative [133]. An AI > 1.5 indicates VZV manifestation within the CNS [134].

NGS might be used to detect pathogens causing CNS infections like VZV. This can lead to earlier, more targeted treatment, accelerating investigation and treatment of neuroinvasive infections (**B-II_{t,u}**) (Table 2) [29,135].

The main treatment for VZV encephalitis is intravenous acyclovir (**A-II_{t,u}**) (Table 3) [132,133]. The recommended empirical intravenous acyclovir therapy is 10 mg/kg BW every 8 h, with a maximum dose of 800 mg per dose in adults, for (7-) 14 days [132,135]. Treatment must be adapted to kidney function. Should the patient's condition normalize, a transition to oral valacyclovir may be recommended. The recommended course of treatment is to continue for a minimum of 14 days (**A-II_{t,u}**) [136]. In cases where VZV infections are unresponsive to acyclovir, foscarnet is administered intravenously (**B-III**) (Table 3) [137, 138]. Immunomodulatory treatments, such as corticosteroids, may be considered to reduce inflammation and prevent further CNS damage in severe cases or in patients with immune-related complications (**C-II_{t,u}**) (Table 3) [113,139].

7.1.7. Other viruses

Other viruses may be detected in the CSF by PCR, e.g., adenovirus, enterovirus, WNV, or Torque teno virus (**A-II_{t,u}**) [28,140]. As for the viruses specified above, CSF mNGS might be used (**B-III**) [141], albeit sometimes the infectious agent might be identified only by standard CSF PCR assays or mNGS only [142,143]. Some of these viruses are considered causative, e.g., as reported for adenoviral meningoencephalitis after HCT [144]. Treatment of these viral CNS infections is mainly symptomatic, while cidofovir might be used to treat adenoviral meningitis (**C-III**) [145].

7.2. Fungi

Fungal CNS infections are serious complications that predominantly affect immunocompromised individuals. IFD are caused by a variety of fungal pathogens, including *Aspergillus* spp., *Mucorales*, *Candida* spp., and *C. neoformans*. Fungi often enter the CNS via hematogenous spread, originating from primary infections in other organs, such as the lungs, or through bloodstream infections, especially in cases involving *C. neoformans* and *Candida* spp. [146]. After invasion of the CNS, fungal cells typically interact with other activated resident brain cells, including microglia, astrocytes, and endothelial cells [147].

Candida spp. cause candidemia and may subsequently invade the CNS, leading to fungal meningitis, meningoencephalitis, or, rarely, brain abscesses [148]. Invasive *Candida* infection of the CNS has been described mostly in pre-term neonates but also occurs in adults during disseminated disease [149]. Since *Candida* CNS infections typically develop from candidemia, ocular complications such as chorioretinitis or endophthalmitis should also be considered. Early ophthalmological assessment is therefore recommended in patients with candidemia, as findings may guide the duration and choice of antifungal therapy. Such considerations likewise apply to other fungal species with potential ocular dissemination.

The most frequently identified mold in IFD of the CNS is *A. fumigatus* [150]. CNS aspergillosis typically presents as single or multiple brain abscesses [148]. Mucormycosis of the CNS often arises from adjacent structures (e.g., the paranasal sinuses), entering the CNS *per continuitatem*. However, hematogenous spread following pulmonary mucormycosis has also been described [150–152].

Overall, IFD of the CNS not only occurs in patients with HOD. Data are also available from other populations, such as people living with HIV (PLWH) or patients with diabetes mellitus [150,153], and randomized clinical trials (RCT) for diagnostic measures and treatment are lacking. Invasive mold infections of the CNS have been more frequently reported in recent years, occasionally related to healthcare-related procedures [153–155], including in HOD [150,156].

Results from cohort studies on risk factors for IFD of the CNS point towards a more frequent involvement of the brain in patients with lung IFD, especially in patients who respond less well to treatment of the underlying hematological malignancy [150]. Several case series of serious IFD of the CNS have been published in patients receiving treatment with Bruton's tyrosine kinase inhibitors (BTKi) [156–158]. It remains to be determined whether BTKi treatment or particular BTKi compounds represent an independent risk factor [159], or a publication/observation bias is present, while some authors have even discussed antifungal prophylaxis during BTKi treatment [160]. Notably, IFD of the brain in patients with HOD seems to occur more frequently in patients with refractory or relapsed disease as well as among those who have received several treatment lines for their malignancy [160]. In patients receiving CAR T-cell therapy, IFD of the CNS have not yet been reported in clinical trials. Mortality of IFD of the CNS is exceedingly high, as well as the rate of neurological sequelae, thus, timely diagnostic confirmation and multidisciplinary management, including ID specialist consultation, radiology, stereotactic/neurosurgical intervention where appropriate, and microbiology are crucial [146,150].

To diagnose IFD of the CNS, no new RCT has been published since the last version of this guideline [2]. Numerous prospective and retrospective cohort studies, as well as case series, have become available. However, evidence on optimal diagnostic approaches and novel diagnostic measures to optimize and accelerate diagnosis remains scarce. Contrast-enhanced radiological examinations with CT or MRI should be performed in cases of neurological symptoms in patients with HOD and even more urgently in patients with a diagnosed IFD at another body site (**A-II_{t,u}**) (Table 4). If procedures are performed to diagnose any IFD of the CNS, the guideline panel recommends using histopathology from a brain or paranasal sinus biopsy with fungal staining, as well as microscopy, fungal culture, biomarkers, and PCR from CSF (Table 4). Tissue

(e.g., using hematoxylin and eosin, periodic acid-Schiff, or Grocott/silver stains) and CSF diagnostics should be combined with biomarker and pan-fungal PCR assays derived from serum (A-II_u) [150].

Several cohort studies have applied mNGS from CSF to diagnose CNS infections. Therefore, the guideline panel decided to include CSF mNGS in the recommendations; if available, it might support the diagnosis (C-III) (Table 4) [161].

For CNS IFI caused by filamentous fungi, especially *Aspergillus* spp., besides neuroimaging, diagnosis is based on histopathology from a brain or paranasal sinus biopsy with fungal staining (A-II_{t,u}) [20], as well as microscopy and fungal culture from CSF (A-II_u) [20,162], galactomannan (GM) from CSF (A-II_u) [20,162], 1–3-β-D-glucan (BDG) from CSF (A-II_{t,u}) [162–164], and a pan-fungal or species-specific PCR from the CSF (B-II_{t,u}) [161,162]. CSF mNGS can be added, if available. However, a lower strength compared to other techniques to diagnose specifically invasive aspergillosis of the brain was reported (C-III) (Table 4) [161,165].

CNS aspergillosis should be treated with voriconazole (A-II_{t,u}) [40,166,167], isavuconazole (A-II_{t,u}) [168,169], or, in rare cases of azole intolerance or pan-azole resistance, liposomal amphotericin B (L-AmB) (B-III) [167,170,171], combined with surgical intervention when feasible and indicated (B-II_{t,u}) (Table 5) [167,172]. Treatment should be administered at therapeutically adequate dosages, and voriconazole plasma levels should be monitored by TDM. Intraventricular L-AmB has been studied and could improve outcomes if azole-resistant *Aspergillus* strains are detected [173]. However, this is based on less reliable data and is not considered a treatment approach that should be routinely performed (C-III) (Table 5).

Diagnostics for *Mucorales* are mainly based on histopathology (A-II_{t,u}) [20,174], culture from CSF or biopsy pan-fungal or species-specific PCR from the CSF (B-II_{t,u}) [20,175,176], or blood (C-III) [177], as well as mNGS from CSF, if available (B-II_{t,u}) [178–180], in addition to

adequate neuroimaging MRI (A-II_{t,u}) (Table 4) [181,182].

CNS mucormycosis should be treated preferably with L-AmB (A-II_{t,u}) [183], or isavuconazole (A-II_{h,u}) [168,184]. For second-line, single treatment with posaconazole (B-III) [185], or in combination with L-AmB is an option (C-III) [186]. Treatment should be given at the highest tolerable doses, and surgery should be performed whenever possible (A-II_{t,u}) (Table 5) [183,186].

Candida CNS infections are extremely rare in adults with HOD [184]. *Candida* infections of the CNS typically manifest as meningoencephalitis or ventriculitis associated with implant devices, like shunts. Rarely, brain abscesses have been reported [20,148,187]. Neuroimaging may show hydrocephalus in *Candida* meningitis. Overall, MRI is more sensitive herein as compared to CT (A-III) [148,188]. However, CT might be performed more easily in intensive care unit patients. Therefore, in critically ill patients, CT is preferred for hydrocephalus monitoring, alternatively transcranial Doppler sonography should be used in such patients to prevent patient transportation. Autopsy may reveal *Candida* micro-abscesses representing meningoencephalitis, while CT and CSF analysis may not always reveal clear pathological findings in this setting [148]. A *Candida*-specific mannan assay from the CSF can be used but is not validated for the diagnosis of CNS candidiasis and is therefore only recommended with a low level of evidence (C-III) [189]. *Candida* spp. can be cultured from CSF; however, the sensitivity of this method is variable, with positive cultures obtained in 40–80 % of cases (A-II_{t,u}) [187,190]. Direct staining of CSF may detect yeasts in approximately 40 % of cases. Elevated levels of BDG can indicate the presence of *Candida* spp. in the CSF and serum [163,191]. Molecular techniques such as CSF PCR may be useful in detecting *Candida* DNA, especially when cultures are negative or inconclusive (C-III) [192]. In rare cases, brain biopsy may be required for a *definite* diagnosis, particularly when non-invasive diagnostic methods fail to provide clarity [193].

mNGS has demonstrated high sensitivity in detecting *Candida* spp. in

Table 4
Diagnosis of selected fungal CNS infections in patients with HOD.

Fungus	Intention	Intervention	SoR/ LoE	References	Comments
<i>Aspergillus</i> spp.	To diagnose CNS aspergillosis	MRI	A-II _{t,u}	[184,255]	Should be considered whenever feasible [40]
		CSF BDG	A-II _{t,u}	[162–164,191,256,257]	
		CSF culture	A-II _{t,u}	[20,162]	
		Brain biopsy/neurosurgical intervention	A-II _{t,u}	[20,184]	
<i>Mucorales</i>	To diagnose CNS mucormycosis	CSF GM	A-II _u	[20,162,258,259]	CT might additionally be done to detect bone involvement
		MRI	A-II _{t,u}	[181,182]	
		Tissue (e.g., histopathology, PCR assays)	A-II _{t,u}	[20,174]	Consider biopsy of lesions from different sites
		CSF PCR	B-II _{t,u}	[20,175,176]	If pan-fungal PCR is positive specific PCR should follow
Candidiasis	To diagnose CNS candidiasis	CSF mNGS	B-II _{t,u}	[178–180]	Few data, mainly micro-abscesses, secondary hydrocephalus
		Blood PCR	C-III	[177]	
		MRI	A-III	[195,260,261]	
		CSF culture	A-II _{t,u}	[187,190]	
Cryptococcus spp.	To diagnose cryptococcal CNS infection	Serum + CSF BDG	B-II _{t,u}	[163,164,191,257]	Few data
		CSF <i>Candida</i> mannan	C-III	[257]	
		CSF PCR	C-III	[192]	
		CSF mNGS	C-III	[29]	
		MRI	A-II _{t,u}	[262–266]	Might be used in selected refractory or unclear cases with focal lesions
		CSF <i>Cryptococcus</i> antigen	A-II _{t,u}	[262,267–270]	
		CSF India ink staining	A-II _{t,u}	[262,268,270,271]	
		CSF culture	B-II _{t,u}	[20,262,268–271]	
		CSF PCR	B-II _{t,u}	[269,271,272]	
		CSF mNGS	C-III	[123,161,268]	
		Brain/paranasal sinus biopsy	C-III	[20,184,273]	

Note. BDG, 1,3-β-D-glucan; CNS, central nervous system; CSF, cerebral spinal fluid; CT, computed tomography; GM, galactomannan; HOD, hematological or oncological diseases; LoE, level of evidence; mNGS, metagenomic next-generation sequencing; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; SoR, strength of recommendation.

Table 5

Treatment options for selected fungal CNS infections in patients with HOD.

Fungus type	Intention	Intervention	SoR/ QoE	References	Comments	
<i>Aspergillus</i> spp.	To treat CNS aspergillosis	Voriconazole	A-II _{t,u}	[40,166,167]	Low CNS penetration	
		Isavuconazole	A-II _{t,u}	[168,169]		
	L-AmB	B-III	[167,274,275]			
	To treat azole-resistant CNS aspergillosis	Neurosurgical intervention	B-II _{t,u}	[40,167,172]	Should be combined with systemic antifungal treatment	
Intraventricular + i.v. L-AmB		C-III	[173,276]			
<i>Mucorales</i>	To treat CNS mucormycosis	L-AmB	A-II _{t,u}	[183]	Might be used as salvage treatment Other combinations such as posaconazole + caspofungin may also be used	
		Isavuconazole	A-II _{h,t}	[168,184]		
	Surgery (if feasible)	A-II _{t,u}	[183,186,277,278]			
	Posaconazole	B-III	[185]			
		Posaconazole + L-AmB	C-III	[186]		
<i>Candida</i> spp.	To treat CNS candidiasis	L-AmB ± 5-FC	A-II _{t,u}	[148,187,195,279]	Might be used as oral step-down treatment, if susceptible	
		Voriconazole	A-III	[148,187,195,280]		
		Fluconazole	B-II _{t,u}	[187,195,280]		
		Echinocandins	D-III	[281]	Poor CNS penetration	
<i>Cryptococcus</i> spp.	To treat CNS cryptococcosis	Single-dose L-AmB + 5-FC + fluconazole	A-II _t	[198,199]	Induction: single-dose L-AmB + 14 days of 5-FC (100 mg/kg/BW/day) + fluconazole (1.200 mg/kg BW/day)	
		High-dose L-AmB + 5-FC	B-II _t	[198,199]	Induction: high-dose L-AmB + 5-FC 100 mg/kg BW/day; this guideline recommends against using regimens based on conventional amphotericin B deoxycholate	
			Oral 5-FC + fluconazole	B-II _t	[282]	Induction
		L-AmB + 5-FC + fluconazole + ventriculo-peritoneal shunt	C-II _{t,u}	[283]	Induction in patients with increased intracranial pressure	
<i>Scedosporium</i> spp.	To treat CNS scedosporiosis	Voriconazole	A-II _{t,u}	[154,155,284–286]		
		Surgical resection (if indicated, in selected cases)	A-III	[285–287]		
		Voriconazole + L-AmB (or other voriconazole-based combination)	C-III	[286]		
<i>Lomentospora</i> spp.	To treat CNS lomentosporiosis	Surgical resection	A-III	[285,286]	If indicated, in selected cases	
		Voriconazole	A-III	[146,170]		
		Voriconazole + L-AmB	B-III	[153]		
		Voriconazole + terbinafine	B-III	[285,286,288]		
<i>Fusarium</i> spp.	To treat CNS fusariosis	Surgical resection	A-II _{t,u}	[153]	If indicated, in selected cases	
		L-AmB	A-II _{t,u}	[153]		
		Voriconazole	A-II _{t,u}	[289]		
		Any antifungal combination therapy	B-III	[289]		

Note. CNS, central nervous system; 5-FC, 5-fluorocytosine; HOD, hematological or oncological diseases; L-AmB, liposomal amphotericin B; LoE, level of evidence; SoR, strength of recommendation.

CSF, especially in cases where traditional diagnostic tests such as CSF culture, PCR, or antigen detection tests are negative (C-III) (Table 4) [29,38,194].

The combination of L-AmB + 5-FC or fluconazole has been suggested as the optimal initial therapy (A-II_{t,u}) [148,187,195]. Voriconazole has been shown to be effective against several *Candida* spp. and has good CNS penetration, which is critical for the treatment of *Candida* infections in the CNS (A-III) [148,187,195]. Treatment should be continued until all symptoms, CSF and radiological abnormalities, if present, have resolved. If possible, infected CNS devices should be removed, including ventricular shunts and drains [195]. The use of echinocandins (e.g., caspofungin or high-dose micafungin) in the treatment of *Candida* infections of the CNS has not been fully investigated (D-III) [196,197]. The poor CNS penetration of these agents must be considered (Table 5) [196]. In the case of a brain abscess, additional drainage or surgical resection should be performed depending on location and size (C-III).

For cryptococcal meningitis, no major novel diagnostic approaches have become available, and therefore recommendations from the last version of this guideline remain unchanged [2]. For CNS cryptococcosis, the AMBITION trial has defined a single-dose L-AmB during induction treatment as the standard of care accompanied by 5-FC and fluconazole

maintenance as implemented previously in WHO standard regimen (A-II_t) [198,199]. As this RCT was conducted in PLWH, the guideline recommends its application in patients with HOD (A-II_t) (Table 5). Intrathecal amphotericin B has been studied in CNS cryptococcosis and may cause neurotoxicity, but therapeutic benefit remains to be determined, thus we only marginally recommend using this strategy (C-II_{t,u}) [200].

In a review of cases of meningitis/encephalitis caused by *Fusarium* spp., treatment with L-AmB was efficacious (A-II_{t,u}) [153], as well as a combination of L-AmB and voriconazole (B-III), while surgery was not associated with an improved outcome [153]. Nonetheless, for selected cases, surgical debridement of abscesses may be warranted and is thus strongly recommended (A-II_{t,u}) (Table 5). Fosmanogepix could serve as a novel therapeutic option (A-II_{t,u}) [201].

Scedosporiosis and lomentosporiosis of the brain have successfully been treated with voriconazole monotherapy in a cohort study from a registry and is therefore recommended (A-III) (Table 5) [146,170]. Furthermore, olorofim is a promising treatment alternative in patients with scedosporiosis/lomentosporiosis of the brain, but this compound is currently in clinical development and is not yet licensed (B-III) [202–204].

7.3. Toxoplasmosis

The most common parasitic CNS infection is caused by the protozoan *Toxoplasma* spp. and nearly exclusively occurs in immunocompromised individuals [205]. The manifest disease is either a reactivation of a preceding infection or a *de novo* infection, and the clinical presentation is highly dependent on the host's immune status. In immunocompromised patients, bradyzoites undergo a conversion process that results in the formation of tachyzoites within the CNS. Consequently, unclear CNS symptoms and otherwise unexplained fever or signs of infection should encourage specific diagnostics and consultation with neurologists [206, 207].

Due to the rarity of the disease, no RCTs on the diagnosis of CNS toxoplasmosis have been published to date. However, larger case series primarily from the field of HCT or from PLWH have been described [208]. Cranial MRI is the preferred neuroimaging method (A-II_{t,u}) [205, 209,210], as *Toxoplasma*-related encephalitis typically manifests as ring-enhancing lesions (Table 6) [205]. A CT can be used as part of emergency diagnostics if an MRI is not immediately available (B-III) [211]. However, the sensitivity here is limited, so a MRI should be performed afterwards as soon as possible (Table 6). Analysis of the CSF using PCR provides a reliable basis for diagnosis and must be performed in every patient suspected of CNS toxoplasmosis (A-II_{t,u}) [205,212]. PCR diagnostics from peripheral blood can supplement CSF analysis (B-II_u) but is naturally less sensitive (Table 6) [213,214]. If available, NGS-based diagnostics from both CSF and peripheral blood can support the diagnosis (C-III) [123]. However, there is still insufficient experience and data on this diagnostic procedure, especially in CSF (Table 6). Antibody-related diagnostics – the standard in non-immunosuppressed hosts – have a very limited value in patients with HOD (Table 6). However, it can also be used in individual cases to confirm the diagnosis (C-II_{t,u}) [205]. Histology has been the gold standard for several years but should be reserved for critical individual cases due to the invasiveness and possible resulting damage (C-II_{t,u}) [215].

Several anti-infective combination therapies have been tested for the treatment of CNS toxoplasmosis, but primarily in PLWH and in individual cases also in allo-HCT patients (Table 7). As the most effective combination, pyrimethamine + sulfadiazine should primarily be used to treat CNS toxoplasmosis in patients with HOD (A-II_t) [216,217]. Alternatively, treatment can also be carried out with pyrimethamine + clindamycin (B-II_t) [218,219]. The combination of clindamycin + azithromycin (C-III) [220], and sulfamethoxazole/trimethoprim (TMP-SMX) was also reported as being sufficient, but may be less effective than the pyrimethamine-based therapies mentioned above (C-II_t) [217,221], (Table 7). Potential drug-drug interactions and side effects in individual patients should always be considered when choosing the anti-infective treatment.

Due to the high morbidity and mortality of CNS toxoplasmosis, weekly screening using PCR from peripheral blood can be considered in high-risk patients, e.g., after allo-HCT or low CD4-positive T-cell counts.

However, the overall sensitivity of this approach is not convincing, as screening is by no means a substitute for the use of prophylaxis with TMP-SMX (A-III) [222,223].

7.4. Bacteria

Bacterial CNS infections result in meningitis, encephalitis, brain abscesses, and subdural empyema, potentially leading to significant neurological damage. Bacteria can enter the CNS via hematogenous spread, invasion from adjacent infections, or direct inoculation following CNS trauma or surgery [19].

As for other CNS infections MRI, not CT, should be the preferred imaging modality (A-II_{h,t}) [39,41,224]. A statistical model identified three significant features for CNS infection in MRI: intracranial enhancement (odds ratio [OR] 3.42; $p = 0.02$), multifocal parenchymal abnormality (OR 3.22; $p = 0.03$), and restricted diffusion (OR 4.01; $p = 0.05$) [224]. With high specificity, PCR from CSF is the preferred method (A-II_{t,u}) [225,226], especially in the acute phase of infection [225]. Gram staining of CSF and cytology is still used and may help to identify bacterial origin very early. In addition, in patients with bacterial CNS infection blood cultures are also often positive (>50 %; with no difference compared to patients without HOD) [19], and blood cultures complement the diagnostics (A-II_{t,u}) [19,41,227]. Especially for antibiotic resistance testing, CSF cultures should be performed – ideally before antibiotic therapy (A-II_{t,u}) [19,24,25,225]. In immunocompromised patients and very old patients, neck stiffness, fever, and even CSF pleocytosis may not be present. CSF granulocytes have a high diagnostic accuracy for bacterial CNS infection. A cutoff at 50 % CSF granulocytes may be helpful with a sensitivity of 94 %, specificity of 80 %, negative predictive value of 98 %, and positive predictive value of 57 % (B-II_{t,u}) [228]. In patients with suspected bacterial CNS infection, Gram staining of the CSF to diagnose a non-purulent CSF with bacterial lawn is highly recommended (A-III) [229]. However, in general, in patients with HOD, a positive CSF Gram-stained smear is found less frequently than in

Table 7

Treatment options for selected parasitic CNS infections in patients with HOD.

Parasitic	Intention	Intervention	SoR/ LoE	References
<i>Toxoplasma</i> spp.	To treat <i>Toxoplasma</i> spp. encephalitis	Pyrimethamine + sulfadiazine	A-II _t	[216,217, 291,292]
		Pyrimethamine + clindamycin	B-II _t	[216,218, 219, 291–294]
		TMP-SMX	C-II _t	[217,221, 292]
		Clindamycin + azithromycin	C-III	[220]

Note. CNS, central nervous system; HOD, hematological or oncological diseases; LoE, level of evidence; SoR, strength of recommendation; TMP-SMX, sulfamethoxazole/trimethoprim.

Table 6

Diagnosis of CNS toxoplasmosis in patients with HOD.

Parasitic	Intention	Intervention	SoR/ LoE	References	Comments
<i>Toxoplasma</i> spp.	To diagnose CNS <i>Toxoplasma</i> spp.	MRI	A-II _{t,u}	[205,209,210]	
		CSF PCR	A-II _{t,u}	[205,209,210,212, 290]	
		PCR blood	B-II _u	[213,214]	
		Blood serology	C-II _{t,u}	[205]	
		CSF NGS	C-III	[123]	
		CNS biopsy	C-II _{t,u}	[215]	Might not be required if CSF PCR positive and typical imaging pattern, can be useful in refractory cases

Note. CNS, central nervous system; CSF, cerebral spinal fluid; HOD, hematological or oncological diseases; LoE, level of evidence; MRI, magnetic resonance imaging; NGS, next-generation sequencing; PCR, polymerase chain reaction; SoR, strength of recommendation.

Table 8

Diagnosis of selected bacterial CNS infections in patients with HOD.

Pathogen	Intention	Intervention	SoR/LoE	Reference	Comments
All	To diagnose bacterial CNS infection	Brain imaging	A-II _{h,t}	[39,41,224]	MRI preferred over CT
		CSF PCR	A-II _{t,u}	[225,226]	Especially in the acute phase
		Blood cultures	A-II _{t,u}	[19,41,227,295]	Also often (>50 %) positive
		CSF cultures	A-II _{t,u}	[19,24,25,225]	Especially for antibiotic resistance testing; before antibiotic therapy
		CSF NGS	B-II _{t,u}	[29]	If available, back-up diagnostics in selected cases

Note. CNS, central nervous system; CSF, cerebral spinal fluid; CT, computed tomography; HOD, hematological or oncological diseases; LoE, level of evidence; MRI, magnetic resonance imaging; NGS, next-generation sequencing; PCR, polymerase chain reaction; SoR, strength of recommendation.

patients without cancer (25.8 % vs. 43.9 %; $p = 0.004$) [19]. If available, NGS of the CSF can be used as back-up diagnostic in selected cases (B-II_{t,u}) [29]. PCR and a Ziehl-Neelsen stain of the CSF should be performed in suspected cases of CNS tuberculosis (A-II_{t,u}) [230,231]. Taken together, different diagnostic tests should always follow the suspected pathogen (A-III) [232]. To differentiate bacterial pleocytosis from other causes of pleocytosis, the CHANCE score (consisting of CSF cell count, CSF protein, CRP, WBC, abnormal mental status, and nuchal rigidity) can be helpful (B-II_{t,u}). However, this score has a low test performance (sensitivity 90–92 %, specificity 76–91 %) [233,234]. The recommendations on the diagnosis of bacterial CNS infections are summarized in Table 8.

In patients with HOD with suspected bacterial meningitis, it is recommended to start antibiotic therapy immediately after blood cultures have been drawn, ideally within one hour after entering the hospital (A-II_{t,u}) [41]. Delay in antibiotic therapy (exceeded 6 h vs. treatment within 2 h of admission) is associated with an unfavorable outcome at discharge (adjusted risk ratio 1.5; $p = 0.03$) [42]. Ideally, the aim is to treat within one hour after admission to hospital. Diagnostic procedures must not delay treatment [235]. In general, in patients with HOD, as in the general population, empirical 3rd generation cephalosporins + ampicillin (+ vancomycin if shunt infection is suspected) would be the antibiotic regimen of choice, and meropenem + linezolid might be considered for nosocomial bacterial CNS infection (B-III) [236].

To lower mortality in patients with HOD and bacterial meningitis,

adjunctive dexamethasone/steroids cannot be recommended in general (C-II_{r,t,u}), because a clear survival benefit could not be demonstrated [25,237]. However, for pneumococcal meningitis, adjunctive steroids reduce morbidity and mortality (B-II_{r,t,u}) [237,238]. The recommendations for the treatment of different bacterial CNS infections are specified in Table 9.

8. Conclusions/outlook

This guideline provides updated, comprehensive, and evidence-based recommendations for the diagnosis and treatment of CNS infections in adult patients with HOD. However, clinical decisions are frequently supported by a low level of evidence. Therefore, such recommendations are important for daily clinical care to help improve patient outcomes in those at high risk of morbidity and mortality. However, due to the common lack of well-designed clinical trials, especially RCTs, in the field addressed here, the recommendations in this guideline are frequently of moderate strength.

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Table 9

Treatment options for selected bacterial CNS infections in patients with HOD.

Pathogen	Intention	Intervention	SoR/LoE	References	Comments
All	To treat bacterial CNS infections	Antibiotics	A-III	[41,42,236]	Start immediately after blood cultures were drawn; options may include ampicillin, vancomycin/linezolid, ceftriaxone, meropenem (based on local epidemiology)
		High-dose antibiotics	A-II _t	[16,296]	
<i>Streptococcus pneumoniae</i> / <i>Haemophilus influenzae</i>	To prevent neurological complications in pneumococcal/ <i>H. influenzae</i> meningitis	Adjunctive steroids	B-II _{r,t}	[230]	Consider primarily in all bacterial encephalitis, should be adapted after isolation of pathogen, useful particular in pneumococcal/ <i>H. influenzae</i> meningitis
<i>Streptococcus pneumoniae</i>	To improve mortality/morbidity in pneumococcal meningitis	Adjunctive steroids	B-II _{r,t,u}	[238]	
<i>Nocardia</i> spp.	To treat CNS nocardiosis	TMP-SMX	A-II _u	[39,230]	Alternatively, linezolid, amikacin, meropenem
<i>Bacillus cereus</i>	To treat CNS <i>B. cereus</i> infection	Vancomycin	A-III	[295]	Should be combined with other antibiotics (e.g., ceftriaxone)
<i>Listeria monocytogenes</i>	To treat <i>L. monocytogenes</i> meningoencephalitis	Ampicillin (+ gentamicin)	A-II _{t,u}	[230,297]	Alternatively high-dose moxifloxacin > 3 weeks (faster bactericidal activity at achievable CNS concentrations) [298]
	To improve outcome in patients with <i>L. monocytogenes</i> meningitis	Adjunctive dexamethasone	A-II _t	[299]	Mortality: OR 0.40 (95 % CI 0.19–0.84); $p = 0.016$
<i>Mycobacterium tuberculosis</i>	To treat CNS tuberculosis	Antibiotic combinations	A-II _{t,u}	[230,300]	2 months isoniazid + rifampicin + ethambutol + pyrazinamide, followed by 9–13 months isoniazid + rifampicin or rifabutin; MDR and XDR: isoniazid + rifampicin or rifabutin + pyrazinamide + ethambutol + moxifloxacin or levofloxacin
	To reduce mortality and adverse effects in CNS tuberculosis	Adjunctive steroids	A-II _{r,t}	[238,301]	

Note. CNS, central nervous system; HOD, hematological or oncological diseases; LoE, level of evidence; MDR, multidrug-resistant; OR, odds ratio; SoR, strength of recommendation; TMP-SMX, sulfamethoxazole/trimethoprim; XDR, extensively drug-resistant; 95 % CI, 95 % confidence interval.

CRedit authorship contribution statement

Rehsan Akdas: Writing – original draft, Formal analysis. **Enrico Schalk:** Writing – original draft, Supervision, Project administration, Formal analysis, Conceptualization. **Jannik Stemler:** Writing – original draft, Formal analysis. **Stefan Schwartz:** Investigation, Formal analysis. **Uta Meyding-Lamadé:** Investigation, Formal analysis. **Jens P. Panse:** Investigation, Formal analysis. **William Krüger:** Investigation, Formal analysis. **Holger Rohde:** Investigation, Formal analysis. **Markus Ruhnke:** Investigation, Formal analysis. **Maximilian Christopeit:** Investigation, Formal analysis. **Klemens Angstwurm:** Investigation, Formal analysis. **Claus P. Heußel:** Investigation, Formal analysis. **Oliver A. Cornely:** Investigation, Formal analysis. **Daniel Teschner:** Writing – original draft, Supervision, Project administration, Formal analysis, Conceptualization. **Martin Schmidt-Hieber:** Writing – original draft, Supervision, Project administration, Formal analysis, Conceptualization.

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