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)

M. Schmidt-Hieber1*, G. Silling2, E. Schalk3, W. Heinz4, J. Panse2, O. Penack5, M. Christopeit6, D. Buchheidt7, U. Meyding-Lamadé8,9,10, S. Hähnel11, H. H. Wolf12, M. Ruhnke13, S. Schwartz14 & G. Maschmeyer15

1Department of Hematology, Oncology and Tumor Immunology, HELIOS Clinic Berlin-Buch, Berlin; 2Department of Hematology, Oncology and Stem Cell Transplantation, University Hospital, Aachen, Medical Faculty, RWTH Aachen, Aachen; 3Department of Hematology and Oncology, Otto-von-Guericke University Hospital Magdeburg, Magdeburg; 4Department of Internal Medicine II, University Hospital Würzburg, Center of Internal Medicine, Würzburg; 5Department of Hematology, Oncology and Tumor Immunology, Charité University Medicine, Campus Virchow Clinic, Berlin; 6Department of Stem Cell Transplantation, University Medical Center Hamburg Eppendorf, Hamburg; 7Department of Hematology and Oncology, Mannheim University Hospital, University of Heidelberg, Mannheim; 8Department of Neurology, Hospital Nordwest Frankfurt, Frankfurt/M., Germany; 9Brunei Neuroscience Stroke and Rehabilitation Centre, Jerudong, Brunei Darussalam; 10Department of Neuroinfectiology, Otto-Meyerhof-Centre, University of Heidelberg, Heidelberg; 11Department of Neuroradiology, University Hospital Heidelberg, Heidelberg; 12Department of Hematology and Oncology, University Hospital Halle, Halle; 13Paracelsus Clinic Osnabrück, Osnabrück; 14Department of Hematology and Oncology, Charité University Medicine, Campus Benjamin Franklin, Berlin; 15Department of Hematology, Oncology and Palliative Care, Ernst von Bergmann Clinic, Potsdam, Germany

Received 3 December 2015; revised 21 March 2016; accepted 24 March 2016

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.

Keywords: 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, ...
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].

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

| (A) | 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) | 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

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.

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

*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.
| Intention | Intervention | SoR | Comments | References |
|-----------|--------------|-----|----------|------------|
| **Toxoplasma spp.** | **To diagnose cerebral toxoplasmosis** | A | Can be combined with isolation of the parasite, e.g. after mouse inoculation or inoculation in tissue cell cultures | [24] |
| | Demonstration of tachyzoites and/or cysts after Wright-Giemsa and/or immuno-peroxidase staining (CSF or biopsy material) | B | Sensitivity 50%–100%, specificity 90%–100%. Should be performed within the first week after initiation of antitoxoplasmic treatment | [25–28] |
| | PCR (CSF) | C | IgG-ELISA is more sensitive than LAT (92% versus 48%) | [29] |
| | IgG-ELISA/LAT (CSF) | D | Negligible value | [29] |
| | IgM-ELISA (CSF) | D | Few data | [25] |
| | LAMP assay (CSF) | D | Few data | [25] |
| **Fungi** | **To detect and specify a fungus obtained from CNS biopsy** | 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] |
| | Paraffin sections of CNS biopsies (e.g. using H&E, PAS, or Grocott/silver stains) | B | No validated cutoff (probably lower than for serum samples), reduced sensitivity under antifungal treatment | [32–36] |
| **To diagnose CNS aspergillosis** | Detection of galactomannan (CSF) | B | No validated cutoff (probably lower than for serum samples), reduced sensitivity under antifungal treatment | [33–37, 41] |
| | PCR (CSF) | B | Sensitivity and specificity 90%–100% (in-house assays) | [32–36] |
| | Fungal cultures (CSF) | B | Positive in ~30% of patients with Aspergillus meningitis | [32–36] |
| | Detection of (1→3)-β-D-glucan (CSF) | C | Few data | [42–43] |
| **To diagnose Candida CNS infection** | 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 *Candida* mannan antigen (CSF) | C | Few data | [46–48] |
| | Detection of (1→3)-β-D-Glucan (CSF) | C | Few data | [43, 49] |
| | PCR (CSF) | C | Few data | [38–50, 52] |
| **To diagnose mucormycosis** | 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 | Few data | [57] |
| | CSF-based diagnostics | D | No valid data | | |
| **To diagnose cryptococcal meningitis** | 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, 60, 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] |
| | Biopsy (culture/histopathology), e.g. after Grocott/silver or Alcian blue staining | C | Required only in selected cases | [60] |
| **Viruses** | **To diagnose HSV encephalitis** | A | Sensitivity and specificity 95%–100% | [64, 65] |
| | PCR (CSF) | A | Sensitivity and specificity of HSV antigen detection ~90%, frequently nonspecific antibodies | [66, 67] |
| | Detection of HSV antigens and antibodies (CSF) | C | Sensitivity and specificity of HSV antigen detection ~90%, frequently nonspecific antibodies | [66, 67] |
| **To diagnose CMV CNS disease** | Culture (CSF) | D | Low sensitivity of culture might be due to inhibiting HSV IgG antibodies | [66, 68, 69] |
| **To diagnose EBV meningoencephalitis** | PCR (CSF) | A | Sensitivity nearly 100% | [70–72] |
| | Culture (CSF) | C | Might only be used as an adjunctive test (sensitivity ~20%) | [69, 72] |
| | 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 | Might be more sensitive than CSF VZV PCR in the case of cerebral VZV vasculopathy [80–82] |
| | Detection of VZV IgG antibodies (CSF) | B | [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] |
| To identify pathogen and perform resistance testing | 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.
| Causative agent | Intention | Intervention | SoR/QoE | Comments | References |
|-----------------|-----------|--------------|---------|----------|------------|
| **Toxoplasma 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 | 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 | [110] |
| | | Pyrimethamine (orally, 100–200 mg load, then 50 mg/day) + clindamycin (orally or i.v., 600 mg q6h) | BII | Pyrimethamine should be combined with folinic acid | [111–113] |
| | | Trimethoprim (10 mg/kg/day)— sulfamethoxazole (orally or i.v.) | BII | | [114] |
| | | Atovaquone (orally, e.g. 750 mg q6h) | BII, 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** | Aspergillus spp. | 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 (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 | [119–126] |
| | - 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] |
| **Candida spp.** | Primary anti-infective treatmentb - to cure - | L-AmB (i.v., ≥5 mg/kg/day, optimal dose unclear) or ABLC (i.v., 5 mg/kg/day) ± 5-FC (i.v., 25 mg/kg q6h)b | BIII | Mainly preclinical data, case reports or small patient series (and data from extracerebral systemic Candida infection) | [140–144] |
| | | Voriconazole (i.v., 6 mg/kg q12h for the first 24 h, then 4 mg/kg q12h) | CIII | If a susceptible Candida spp. has been isolated and the patient is clinically stable and not neutropenic and had no prior azole exposure | [145, 146] |
| | | Fluconazole (i.v., loading dose 800 mg/day, then 400 mg/day) | CIII | Unfavorable toxicity profile | [44, 135, 147, 149, 150] |
| | | D-AmB | DIII | Mainly preclinical data and few case reports | [151–153] |
| | | Caspofungin, micafungin, anidulafungin | DIII | | |
**Mucorales**

**Primary treatment**

- **Surgery**
- **L-AmB (i.v., ≥5 mg/kg/day, optimal dose unclear, up to 10 mg/kg/day has been used)**
- **Reduction of immunosuppression**
  - **ABLC** (i.v., 5 mg/kg/day)
  - **L-AmB (i.v., ≥5 mg/kg/day) + caspofungin (i.v., 50–70 mg/day)**

**Salvage treatment**

- **D-AmB**
- **Posaconazole (preferable i.v., 300 mg q12h for the first 24 h, then 300 mg/day)**
- **Itraconazole (orally or i.v., higher dosages of up to 800 mg/day might be used)**

**Cryptococcus spp.**

**Primary treatment**

- **L-AmB (i.v., 3–4 mg/kg/day) or ABLC** (i.v., 5 mg/kg/day) + 5-FC (i.v., 25 mg/kg q6h)
- **D-AmB (i.v., 0.7–1.0 mg/kg/day) + 5-FC (i.v., 25 mg/kg q6h)**
- **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)**
- **L-AmB (i.v., 3 mg/kg/day)**
- **D-AmB (i.v., 0.7–1.0 mg/kg/day) + fluconazole (preferable i.v., 800–1200 mg/day)**
- **Voriconazole (preferable i.v., 6 mg/kg q12h for the first 24 h, then 4 mg/kg q12h)**
- **ABLC** (i.v., 5 mg/kg/day)
- **Fluconazole (preferable i.v., loading dose 1200 mg/day, then 800 mg/day + 5-FC (i.v., 25 mg/kg q6h)**

**Salvage treatment**

- **Voriconazole (preferable i.v., 6 mg/kg q12h for the first 24 h, then 4 mg/kg q12h)**
- **Posaconazole (preferable i.v., 300 mg q12h for the first 24 h, then 300 mg/day)**

**Viruses**

**Primary or salvage treatment**

- **Caspofungin, micafungin, anidulafungin**

---

Should be considered whenever possible

Treatment delay may enhance mortality, response rate 80%–95%

No comparative data, not always feasible

Around 70% response rate

Low CNS penetration, dosages up to 3200 mg/day have been used

Might be used for extended cases or patients refractory to single-agent treatment

Low CNS penetration

Unfavorable toxicity profile

Might be combined with caspofungin or L-AmB

• Induction therapy for at least 4 weeks, might be followed by consolidation with fluconazole (400 mg/d) at least 8 weeks

• Consider unfavorable toxicity profile of D-AmB

Study performed in Malawi with limited economic resources

Clinical efficacy rate ~40%

Clinical efficacy rate ~50%

No relevant activity
| Causative agent | Intention | Intervention | SoR/QoE | Comments | References |
|----------------|-----------|--------------|---------|----------|------------|
| HSV            | Primary or salvage treatment | Aciclovir (i.v., 10 mg/kg q8h) | AIII | Treatment duration at least 2–3 weeks<sup>e</sup> | [2, 73, 185–189] |
|                | - to cure - | Foscarnet (i.v., 60 mg/kg q8h or 90 mg/kg q12h) | CIII | Might be used in refractory cases | [190] |
|                |           | Valaciclovir (orally, 1 g q8h) | CIII | Might be used as continuation therapy | [191–194] |
| CMV            | Primary or salvage treatment | 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] |
|                | - to cure - | Ganciclovir (i.v., 5 mg/kg q12h) + foscarnet (i.v., 60 mg/kg q8h or 90 mg/kg q12h) | BIII | | [188, 193–197] |
|                |           | 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] |
|                |           | Foscarnet (i.v., 60 mg q8h or 90 mg/kg q12h) + cidofovir (i.v., e.g. 5 mg/kg once weekly) | CIII | | [195, 201] |
| EBV (meningoencephalitis) | Primary or salvage treatment | Reduction of immunosuppression | AIII | Might not always be possible | [188, 202] |
|                | - to cure - | Ganciclovir (i.v., 5 mg/kg q12h) | BIII | Valganciclovir (orally) has also been used | [202–207] |
| HHV-6          | Primary or salvage treatment | Aciclovir (i.v., 10 mg/kg q8h) | CIII | Few reports with success published | [208, 209] |
|                | - to cure - | 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] |
|                |           | Cidofovir (i.v., e.g. 5 mg/kg once weekly) | CIII | | [78, 214] |
| VZV            | Primary or salvage treatment | Aciclovir (i.v., 10 mg/kg q8h)<sup>f</sup> | AIII | Inefficacy has been reported | [2, 73, 216–218] |
|                | - to cure - | Aciclovir (i.v., 10 mg/kg q8h) + foscarnet (i.v., 60 mg/kg q8h or 90 mg/kg q12h) | CIII | | [219] |
| JC virus (PML) | Primary or salvage treatment | Ganciclovir (i.v., 5 mg/kg q12h) | CIII | Not always possible | [188, 220] |
|                | - to cure - | Reduction of immunosuppression | AIII | | [12] |
| Bacteria       | To reduce mortality and neurologic defects | Empiric treatment | AII<sub>n</sub> | | [107, 222, 223] |
|                |           | Dexamethasone (e.g. 0.15 mg/kg q6h for the first 4 days) | CII<sub>n</sub> | Should be started with first dose of antibiotics if it is used | [224, 225] |
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 into 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] [110]. Pyrimethamine in combination with clindamycin [BII] or single-agent trimethoprim-sulfamethoxazole [BII] 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,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 infarction 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 [AIIa] [117, 118, 240]. Amphotericin B deoxycholate (D-AmB) should be avoided due to its poor tolerability and negligible efficacy [DIIu], 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 intral esional 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 [BIIu] [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 [AIHb], 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 [AIHb] [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 [DIII] [253]. Posaconazole [BIII] or isavuconazole [CHI] 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] [171, 172, 181, 260]. Voriconazole or posaconazole may be used for salvage treatment [CIII] [132, 180, 183]. Cryptococcus spp. are in vitro resistant to echinocandines [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] [73, 185–187].

In rare cases of aciclovir resistance, foscamet 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 foscamet [AIII] [188]. Some authors recommend a combination of both agents [BIII] [188, 195–197]. Cidofovir as single agent or in combination with foscarinet 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 encephalitis 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 foscarinet 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...
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 [DIIa] [12, 221]. Several experimental approaches such as adoptive T-cell therapy or administration of interleukin-2, melphalan or mitrazapine 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.

acknowledgements

The authors thank Martin Skalej and Anja Lenz (Institute of Neuroradiology, Otto-von-Guericke University Hospital Magdeburg, Magdeburg, Germany) and Hans-Christian Bauknecht for providing MRI images (see supplementary Material, available at Annals of Oncology online).

funding

None. Travel expenses and costs for group meetings were reimbursed by the German Society for Hematology and Medical Oncology (DGHO).

disclosure

GS: grant/research support: MSD Sharp & Dohme, Pfizer, Gilead Sciences, Astellas Pharma; consultant: MSD Sharp & Dohme, Basilea Pharmaceutica. WH: research grants: MSD Sharp & Dohme, Merck, Pfizer; speakers bureaus: Alexion Pharmaceuticals, Astellas Pharma, Basilea Pharmaceutica, Bristol-Myers Squibb, Chugai Pharmaceutical, Gilead Sciences, Janssen-Cilag, MSD Sharp & Dohme, Pfizer; travel grants: Alexion Pharmaceuticals, Astellas Pharma, MSD Sharp & Dohme, Novartis Pharma, Pfizer.
references

1. Denier C, Boursis J, Lacroc'X C et al. Spectrum and prognosis of neurologic complications after hematopoietic transplantation. Neurology 2006; 67(11): 1990–1997.
2. Schmidt-Hieber M, Schwender J, Heinz WJ et al. Viral encephalitis after allogeneic stem cell transplantation: a rare complication with distinct characteristics of different causative agents. Haematologica 2011; 96(1): 142–149.
3. Ullmann AJ, Comely OA, Donnelly JP et al. ESCMID guideline for the diagnosis and management of Candida diseases 2012: developing European guidelines in clinical microbiology and infectious diseases. Clin Microbiol Infect 2012; 18 (Suppl 7): 1–8.
4. Bleggi-Torres LF, de Medeiros BC, Werner B et al. Neuropathological findings after bone marrow transplantation: an autopsy study of 180 cases. Bone Marrow Transplant 2000; 25(3): 301–307.
5. Sostak P, Padovan CS, Yousry TA et al. Prospective evaluation of neurological complications after allogeneic bone marrow transplantation. Neurology 2003; 60 (5): 842–848.
6. Macchle M, Dietrich U, Prumbaum M et al. Opportunistic CNS infection after bone marrow transplantation. Bone Marrow Transplant 1999; 23(11): 1167–1176.
7. Vu T, Carrum G, Hutton G et al. Human herpesvirus-6 encephalitis following allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant 2007; 39(11): 705–709.
8. Skida A, Lantennier F, Groll AH et al. Diagnosis and treatment of mucormycosis in patients with hematological malignancies: guidelines from the 3rd European Conference on Infections in Leukaemia (ECL 3). Haematologica 2012; 98(4): 492–504.
9. Roden MM, Zaudits TE, Buchanan WL et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis 2005; 41(5): 634–653.
10. Skida A, Pagano L, Groll A et al. Zygomyces in Europe: analysis of 230 cases accrued by the registry of the European Confederation of Medical Mycology (ECMM) Working Group on Zygomycosis between 2005 and 2007. Clin Microbiol Infect 2011; 17(12): 1859–1867.
11. Carson KR, Evans AM, Richley EA et al. Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the Research on Adverse Drug Events and Reports project. Blood 2009; 113(20): 4834–4840.
12. Khurafan-Dabaja MA, Ayala E, Greene J et al. Two cases of progressive multifocal leukoencephalopathy after allogeneic hematopoietic cell transplantation and a review of the literature. Bone Marrow Transplant 2007; 39(2): 101–107.
13. Sommers LM, Hawkins DS. Meningitis in pediatric cancer patients: a review of forty cases from a single institution. Pediatr Infect Dis J 1999; 18(10): 902–907.
14. Salfieh JE, Mead PA, Sepkowitz KA et al. Bacterial and fungal meningitis in patients with cancer. Neurology 2008; 70(12): 943–947.
15. Wang X, Dong Y, Qi X et al. Clinical review: efficacy of antimicrobial-impregnated catheters in external ventricular drainage—a systematic review and meta-analysis. Curr Care 2013; 17(4): 234.
16. Neumann S, Krause SW, Mischmeyer G et al. Primary prophylaxis of bacterial infections and Pneumocystis jirovecii pneumonia in patients with hematological malignancies and solid tumors: Guidelines of the Infectious Diseases Working Party (AGIKO) of the German Society of Hematology and Oncology (DGHO). Ann Hematol 2013; 92(4): 433–442.
17. Tacke D, Buchheidt D, Karthaus M et al. Primary prophylaxis of invasive fungal infections in patients with haematologic malignancies. 2014 update of the recommendations of the Infectious Diseases Working Party of the German Society for Haematology and Oncology. Ann Hematol 2014; 93(4): 1449–1456.
18. Pruitt AA. Central nervous system infections in cancer patients. Semin Neurol 2010; 30(3): 296–310.
19. Cunha BA. Central nervous system infections in the compromised host: a diagnostic approach. Infect Dis Clin North Am 2001; 15(2): 567–590.
20. Gazzinelli RT, Elloum I, Wynn TA, Sher A. Acute cerebral toxoplasmosis is induced by in vivo neutralization of TNF-alpha and correlates with the down-regulated expression of inducible nitric oxide synthase and other markers of macrophage activation. J Immunol 1993; 151(7): 3672–3681.
21. Walsh TJ, Groll AH. Emerging fungal pathogens: evolving challenges to immunocompromised patients for the twenty-first century. Transpl Infect Dis 1999; 1(4): 247–261.
22. Wheat LJ, Musial CE, Jenny-Avital E. Diagnosis and management of central nervous system histoplasmosis. Clin Infect Dis 2005; 40(6): 844–852.
23. Rock RB, Olito M, Baker CA et al. Central nervous system tuberculosis: pathogenesis and clinical aspects. Clin Microbiol Rev 2008; 21(2): 243–261.
24. Montoya JG. Laboratory diagnosis of Toxoplasma gondii infection and toxoplasmosis. J Infect Dis 2002; 185(Suppl 1): 573–582.
25. Mkita K, Maeda T, Ono T et al. The utility of cerebrospinal fluid for the molecular diagnosis of toxoplasmosis. Diagn Microbiol Infect Dis 2013; 75(2): 155–159.
26. Vidal JE, Colombo FA, de Oliveira AC et al. PCR assay using cerebrospinal fluid for diagnosis of cerebral toxoplasmosis in Brazilian AIDS patients. J Clin Microbiol 2004; 42(10): 4765–4768.
27. Alfonso Y, Fraia J, Cox R et al. Conventional polymerase chain reaction for the diagnosis of neurotoxoplasmosis: comparison of three sets of primers for the B1 gene using CSF samples. Diagn Microbiol Infect Dis 2013; 75(2): 150–154.
28. Arselimo LM, Vilar FC, Lima JE et al. Usefulness and limitations of polymerase chain reaction in the etiologic diagnosis of neurotoxoplasmosis in immunocompromised patients. J Neurol Sci 2014; 346(1-2): 231–234.
29. Chandramukhi A. Diagnosis of neurotoxoplasmosis by antibody detection in cerebrospinal fluid (CSF) fluid using Lates Agglutination Test and ELISA. J Comm Dis 2004; 36(3): 153–158.
30. Hayden RT, Qian X, Procop GW et al. In situ hybridization for the identification of filamentous fungi in tissue section. Diagn Mol Pathol 2002; 11(2): 119–126.
31. Sundaram C, Umabala P, Laxmi V et al. Pathology of fungal infections of the central nervous system: 17 years’ experience from Southern India. Histopathology 2006; 49(4): 396–405.
32. Antinori S, Corbellino M, Meroni L et al. Aspergillus meningitis: a rare clinical manifestation of central nervous system aspergillosis. Case report and review of 92 cases. J Infect 2013; 66(3): 218–238.
33. Verweij PE, Brinkman K, Kremer HP et al. Aspergillus meningitis: diagnosis by non-culture-based microbiological methods and management. J Clin Microbiol 1999; 37(4): 1186–1189.
34. Viscosi C, Machetti M, Gazzola P et al. Aspergillus galactomannan antigen in the cerebrospinal fluid of bone marrow transplant recipients with probable cerebral aspergillosis. J Clin Microbiol 2002; 40(4): 1496–1499.
35. Soeffker G, Wichmann D, Loderstaedt U et al. Aspergillus galactomannan antigen for diagnosis and treatment monitoring in cerebral aspergillosis. Prog Transplant 2013; 23(1): 71–74.
36. Klontz RR, Menink-Kersten MA, Verweij PE. Utility of Aspergillus antigen detection in specimens other than serum specimens. Clin Infect Dis 2004; 39(10): 1467–1474.

37. Reinwald M, Buchheidt D, Hummel M et al. Diagnostic performance of an Aspergillus-specific nested PCR assay in cerebrospinal fluid samples of immunocompromised patients for detection of central nervous system aspergillosis. PLoS One 2013; 8(2): e56706.

38. Badie P, Albori A. Assessment of a real-time PCR method to detect human non-cryptococcal fungal meningitis. Arch Iran Med 2011; 14(6): 381–384.

39. Kami M, Ogawa T, Kanda Y et al. Early diagnosis of central nervous system aspergillosis using polymerase chain reaction, latex agglutination test, and enzyme-linked immunosorbent assay. Br J Haematol 1999; 106(2): 536–537.

40. Komatsu H, Fujisawa T, Inui A et al. Molecular diagnosis of cerebral aspergillosis by sequence analysis with panfungal polymerase chain reaction. J Pediatr Hematol Oncol 2004; 26(1): 40–44.

41. Hummel M, Spiess B, Kentouche K et al. Detection of Aspergillus DNA in cerebrospinal fluid from patients with cerebral aspergillosis by a nested PCR assay. J Clin Microbiol 2006; 44(11): 3989–3993.

42. Mikulecka M, Murfaro E, Del Bono V et al. (1–3)-β-D-Glucan in cerebrospinal fluid is useful for the diagnosis of central nervous system fungal infections. Clin Infect Dis 2013; 56(10): 1511–1512.

43. Salvatore CM, Chen TK, Toussi SS et al. (1–3)-β-D-Glucan in cerebrospinal fluid as a biomarker for Candida and aspergillus infections of the central nervous system in pediatric patients. J Pediatric Infect Dis Soc 2015; March 19 [epub ahead of print]. doi: 10.1093/jpids/piv014.

44. Sánchez-Portocarrero J, Pérez-Cecilia E, Corral O et al. The central nervous system: therapeutic and diagnostic considerations. Clin Infect Dis 1995; 20(2): 414–420.

45. Voice RA, Bradley SF, Sangeorzan JA, Kauffman CA. Chronic candidal meningitis: an uncommon manifestation of candidiasis. Clin Infect Dis 1994; 19(1): 60–66.

46. Verduyn Lunel FM, Voss A, Kuijper EJ et al. Detection of the β-D-glucan in cerebrospinal fluid of patients suspected of having Candida meningitis. J Clin Microbiol 2004; 42(2): 867–870.

47. Biesbroek JM, Verduyn Lunel FM, Kragt JJ et al. Culture-negative Candida meningitis diagnosed by detection of Candida mannan in CSF. Neurology 2013; 81(17): 1555–1556.

48. Ikeda K, Yamashita J, Fujisawa H, Fujita S. Cerebral granuloma and meningitis caused by Candida albicans: useful monitoring of mannan antigen in cerebrospinal fluid. Neurosurgery 1990; 26(5): 860–863.

49. Lyons JL, Erkkinen MG, Vodopivec I. Cerebrospinal fluid β-D-glucan in isolated Candida meningitis. Clin Infect Dis 2015; 60(1): 161–162.

50. Ralph ED, Hussain Z. Chronic meningitis caused by Candida albicans in a liver transplant recipient: usefulness of the polymerase chain reaction for diagnosis and for monitoring treatment. Clin Infect Dis 1996; 23(1): 191–192.

51. Elsayed S, Fitzgerald V, Massey V, Hussain Z. Evaluation of the Candigen antigen system in pediatric patients. J Pediatric Infect Dis Soc 2015; March 19 [epub ahead of print]. doi: 10.1093/jpids/piv014.

52. Sow D, Tine RC, Sylla K et al. Cryptococcal meningitis in Senegal: epidemiology, laboratory findings, therapeutic and outcome of cases diagnosed from 2004 to 2011. Mycopathologia 2013; 176(5-6): 443–449.

53. Huang H, Fan L, Rajbanshi B, Xu J. Evaluation of a new cryptococcal antigen lateral flow immunoassay in serum, cerebrospinal fluid and urine for the diagnosis of cryptococcosis: a meta-analysis and systematic review. PLoS One 2015; 10(5): e0127117.

54. Aurelius E, Johansson B, Sköldenberg B et al. Rapid diagnosis of herpes simplex encephalitis by nested polymerase chain reaction assay of cerebrospinal fluid. Lancet 1991; 337(8735): 189–192.

55. Lakeman FD, Whitley RJ. Diagnosis of herpes simplex encephalitis: application of polymerase chain reaction to cerebrospinal fluid from brain-biopsied patients and correlation with disease. National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. J Infect Dis 1995; 171(4): 857–863.

56. Whitley RJ, Lakeman F. Herpes simplex virus infections of the central nervous system: therapeutic and diagnostic considerations. Clin Infect Dis 1995; 20(2): 414–420.

57. Lakeman FD, Koga J, Whitley RJ. Detection of antigen to herpes simplex virus in cerebrospinal fluid from patients with herpes simplex encephalitis. J Infect Dis 1987; 155(6): 1172–1178.

58. Fening SW, Esper F, Scholl D, Huang YT. HSV IgG antibody inhibits virus detection in CSF. J Clin Virol 2012; 55(2): 164–167.

59. Bolvin G. Diagnosis of herpesvirus infections of the central nervous system. Herpes 2004; 11(Suppl 2): 48A–56A.

60. Arribas JR, Clifford DB, Fichtenbaum CJ et al. Level of cytomegalovirus (CMV) DNA in cerebrospinal fluid of subjects with AIDS and CMV infection of the central nervous system. J Infect Dis 1995; 172(2): 527–531.

61. Arribas JR, Storch GA, Clifford DB, Tselis AC. Cytomegalovirus encephalitis. Ann Intern Med 1996; 125(7): 577–587.

62. Zhang F, Tetu S, Wang XP et al. Detection of human cytomegalovirus p67 late gene transcripts in cerebrospinal fluid of human immunodeficiency virus type 1-infected patients by nucleic acid sequence-based amplification. J Clin Microbiol 2000; 38(5): 1929–1925.

63. Wu M, Huang F, Jiang X et al. Herpesvirus-associated central nervous system diseases after allogeneic hematopoietic stem cell transplantation. PLoS One 2013; 8(10): e77805.

64. Drago L, Lombardi A, de Vecchi E et al. Comparison of nested PCR and real time PCR of Herpesvirus infections of central nervous system in HIV patients. BMC Infect Dis 2004; 4: 55.

65. Gaeta A, Verzaro S, Cristina LM et al. Diagnosis of neurological herpesvirus infections: real time PCR in cerebral spinal fluid analysis. New Microbiol 2009; 32(4): 333–340.

66. Barberi W, Perone S, Iori AP et al. Proven Epstein-Barr encephalitis with negative EBV-DNA load in cerebrospinal fluid after allogeneic hematopoietic stem cell transplantation in a child with acute lymphoblastic leukemia. Pediatr Transplant 2015; 19(1): E19–E24.

67. Zerr DM. Human herpesvirus 6 and central nervous system disease in hematopoietic cell transplantation. J Clin Virol 2006; 37(Suppl 1): S52–S56.

68. Bhanushali MJ, Kranick SM, Freeman AF et al. Human herpesvirus 6 virus encephalitis complicating allogeneic hematopoietic stem cell transplantation. Neurology 2013; 80(16): 1494–1500.

69. Hill JA, Boech J, Sediak RH et al. Human herpesvirus 6 can be detected in cerebrospinal fluid without associated symptoms after allogeneic hematopoietic stem cell transplantation. J Clin Virol 2014; 61(2): 289–292.

70. Puchhammer-Stöckl E, Popov-Kraupp T, Heinz FX et al. Detection of varicella-zoster virus DNA by polymerase chain reaction in the cerebrospinal fluid of
patients suffering from neurological complications associated with chicken pox or herpes zoster. J Clin Microbiol 1991; 29(7): 1513–1516.
81. Bergström T. Polymerase chain reaction for diagnosis of varicella zoster virus central nervous system infections without skin manifestations. Scand J Infect Dis Suppl 1996; 100: 41–45.
82. Corral I, Querida C, Antela A et al. Neurological complications of varicella-zoster virus in human immunodeficiency virus-infected patients: changes in prevalence and diagnostic utility of polymerase chain reaction in cerebrospinal fluid. J Neurovirol 2003; 9(1): 129–135.
83. Nagel MA, Forghani B, Mahalingam R et al. The value of detecting anti-VZV IgG antibody in CSF to diagnose VZV vasculopathy. Neurology 2007; 68(13): 1069–1073.
84. Gilden D. Varicella zoster virus and central nervous system syndromes. Herpes 2004; 11(Suppl 2): 98A–99A.
85. Nagel MA, Cohrs RJ, Mahalingam R et al. The varicella zoster virus vasculopathies: clinical, CSF, imaging, and virologic features. Neurology 2008; 70(11): 855–860.
86. Berger JR, Aksamit AJ, Clifford DB et al. PML diagnostic criteria: consensus statement from the AAN Neuroinfectious Disease Section. Neurology 2013; 80(15): 1430–1438.
87. McGuire D, Barhite S, Holland H, Miles M. JC virus DNA in cerebrospinal fluid of human immunodeficiency virus-infected patients: predictive value for progressive multifocal leukoencephalopathy. Ann Neurol 1995; 37(3): 395–399.
88. Korálník U, Boden D, Mai Vx et al. JC virus DNA load in patients with and without progressive multifocal leukoencephalopathy. Neurology 1999; 52(2): 253–260.
89. de Luca A, Cingolani A, Linzalone A et al. Improved detection of JC virus DNA in cerebrospinal fluid for diagnosis of AIDS-related progressive multifocal leukoencephalopathy. J Clin Microbiol 1996; 34(5): 1343–1346.
90. Marozcchetti A, Di Giambenedetto S, Cingolani A et al. Reduced rate of diagnostic positive detection of JC virus DNA in cerebrospinal fluid in cases of suspected progressive multifocal leukoencephalopathy in the era of potent antiretroviral therapy. J Clin Microbiol 2005; 43(8): 4175–4177.
91. Bohr V, Rasmussen N, Hansen B et al. 875 cases of bacterial meningitis: diagnostic procedures and the impact of preadmission antibiotic therapy. Part III. J Infect 1993; 7(3): 193–202.
92. Brouwer MC, Tunkel AR, van de Beek D. Epidemiology, diagnosis, and antimicrobial treatment of acute bacterial meningitis. Clin Microbiol Rev 2010; 23(3): 467–492.
93. Michael B, Menezes BF, Cunha J. et al. Effect of delayed lumbar punctures on the diagnosis of acute bacterial meningitis in adults. Emerg Med J 2010; 27(6): 433–438.
94. Nigrovic LE, Malley R, Macias CG et al. Effect of antibiotic pretreatment on cerebrospinal fluid profiles of children with bacterial meningitis. Pediatrics 2008; 122(4): 726–730.
95. Shaneem S, Vinnod Kumar CS, Neelagund YF. Bacterial meningitis: rapid diagnosis and microbial profile: a multicentered study. J Commun Dis 2008; 40(2): 111–120.
96. Thwaites GE, Chau TT, Stepniewska K et al. Diagnosis of adult tuberculous meningitis by use of clinical and laboratory features. Lancet 2002; 360(9342): 122(4): 726.
97. Weenink JJ, Weenink AG, Geerlings SE et al. Severe cerebral toxoplasma infection during 2005–2012 in Turkey. A multicenter prospective surveillance study. Hum Vaccin Immunother 2014; 10(8): 2706–2712.
98. Schroeder PC, Post MJ, Oschatz E et al. Analysis of the utility of diffusion-weighted MRI and apparent diffusion coefficient values in distinguishing central nervous system toxoplasmosis from lymphoma. Neuroradiology 2006; 48(10): 715–720.
99. Shankar SK, Mahadevan A, Kooker JM. Neuropathology of viral infections of the central nervous system. Neuroimaging Clin N Am 2008; 18(1): 19–39.
100. Weenink JJ, Weenink AG, Geerlings SE et al. Severe cerebral toxoplasma infection cannot be excluded by a normal CT scan. Neth J Med 2009; 67(4): 150–152.
101. Shyam babu C, Satchischandra P, Mahadevan A et al. Usefulness of stereotactic biopsy and neuroimaging in management of HIV-1 Clade C associated focal brain lesions with special focus on cerebral toxoplasmosis. Clin Neuroradiol 2013; 115(7): 995–1002.
102. Tseng J, Su Y, Lee M et al. Clinical usefulness of FDG PET/CT in the detection of unusual central nervous system infections. J Neurol Sci 2014; 345(1-2): 244–247.
103. Minder JR, Heegaard W, Mapes A, Brios M. Presentation, time to antibiotics, and mortality of patients with bacterial meningitis at an urban county medical center. J Emerg Med 2001; 21(4): 387–392.
104. Delphi NIS, Lewis RE, Kontoyiannis DP. Delaying amphotericin B-based frontline therapy significantly increases mortality among patients with hematologic malignancy who have zygoencymosis. Clin Infect Dis 2008; 47(4): 503–509.
105. Schmidt-Hieber M, Zweiger J, Uhart KL et al. Central nervous system infections in immunocompromised patients: update on diagnostics and therapy. Leuk Lymphoma 2009; 50(1): 24–36.
106. Kattama C, de Witt S, O’Doherty E et al. Pyrimehmine-sulfadiazine as acute and long-term therapy for toxoplasma encephalitis in patients with AIDS. Clin Infect Dis 1996; 22(2): 268–275.
107. Dannemann B, McCutchan RA, Israeloti D et al. Treatment of toxoplasma encephalitis in patients with AIDS. A randomized trial comparing pyrimethamine plus clindamycin to pyrimethamine plus sulfadiazine. The California Collaborative Treatment Group. Ann Intern Med 1992; 116(1): 33–43.
108. Poppa GJ, Bini T, Gregus G et al. A retrospective study of primary and maintenance therapy of toxoplastic encephalopathies with oral clindamycin and pyrimethamine. Eur J Clin Microbiol Infect Dis 1991; 10(3): 187–189.
109. Kattama C, Evaluation of the efficacy and safety of clindamycin plus pyrimethamine for induction and maintenance therapy of toxoplastic encephalopathies in AIDS. Eur J Clin Microbiol Infect Dis 1991; 10(3): 189–191.
110. Torre D, Casari S, Spenza F et al. Randomized trial of trimethoprim-sulfamethoxazole versus pyrimethamine-sulfadiazine for therapy of toxoplasma encephalitis in patients with AIDS. Italian Collaborative Study Group. Antimicrob Agents Chemother 1998; 42(6): 1346–1349.
111. Kattama C, Mouhton B, Goordon D et al. Atovaquone as long-term suppressive therapy for toxoplasma encephalitis in patients with AIDS and multiple drug intolerance. Atovaquone Expanded Access Group. AIDS 1996; 10(10): 1107–1112.
112. Chirgwin K, Hafner R, Leport C et al. Randomized phase II trial of atovaquone with pyrimethamine or sulfadiazine for treatment of toxoplasma encephalitis in patients with acquired immunodeficiency syndrome: ACTG 237/ANRS 039 Study. AIDS Clinical Trials Group 237/Agence Nationale de Recherche sur le SIDA, Essai 039. Clin Infect Dis 2002; 34(9): 1243–1250.
113. Schwartz S, Ruhnke M, Ribaud P et al. Improved outcome in central nervous system aspergillosis, using voriconazole treatment. Blood 2005; 106(8): 2641–2645.
114. Schwartz S, Reisman A, Troke PF. The efficacy of voriconazole in the treatment of 192 fungal central nervous system infections: a retrospective analysis. Infection 2011; 39(3): 201–210.
115. Coleman JM, Hogg GG, Rosenfeld JV, Waters KD. Invasive central nervous system aspergillosis: cure with liposomal amphotericin B, itraconazole, and radical surgery—case report and review of the literature. Neurosurgery 1995; 36(4): 858–863.
116. Carlini A, Angelini D, Burrows L et al. Cerebral aspergillosis: long term efficacy and safety of liposomal amphotericin B in kidney transplant. Nephrol Dial Transplant 1998; 13(10): 2659–2661.
117. Ng A, Gadon N, Kealey A et al. Successful treatment of aspergillosis brain abscess in a child with acute lymphoblastic leukemia. Pediatr Hematol Oncol 2000; 17(6): 497–504.
221. Poscher ME. Successful treatment of varicella zoster virus meningoencephalitis
220. Tauro S, Toh V, Osman H, Mahendra P. Varicella zoster meningoencephalitis
219. Rottenstreich A, Oz ZK, Oren I. Association between viral load of varicella zoster
218. Suzuki J, Ashizawa M, Okuda S et al. Varicella zoster virus meningoencephalitis
217. Hackanson B, Zeiser R, Bley TA et al. Fatal varicella zoster virus encephalitis in
216. Zerr DM, Gupta D, Huang M et al. Effect of antivirals on human herpesvirus 6
215. Seeley WW, Marty FM, Holmes TM et al. Post-transplant acute limbic
214. Dewhurst S. Human herpesvirus type 6 and human herpesvirus type 7 infections
213. van de Beek D, Brouwer MC, Thwaites GE, Tunkel AR. Advances in treatment of
212. Leport C, Bastuji-Garin S, Perronne C et al. An open study of the pyrimethamine-
211. Schwartz S, Ruhnke M. Aspergillus sinusitis and cerebral aspergillosis. In Latgé
210. Roemer E, Blau IW, Basara N et al. Toxoplasmosis, a severe complication in
209. Downloaded from https://academic.oup.com/annonc/article-abstract/27/7/1207/1741476

by guest
on 30 July 2018
255. Kaide CG, Khandelwal S. Hyperbaric oxygen: applications in infectious disease. Emerg Med Clin North Am 2008; 26(2): 571–595.

256. Almann M, Imran H, Estrada B, Siddiqui AH. Successful treatment of rhino-orbital mucormycosis with posaconazole and hyperbaric oxygen therapy. Pediatr Hematol Oncol 2013; 30(3): 184–186.

257. Pagano L, Fianchi L, Caramatti C et al. Cryptococcosis in patients with hematologic malignancies. A report from GMENA-infection. Haematologica 2004; 89(7): 852–856.

258. Pagano L, Fianchi L, Leone G. Fungal pneumonia due to molds in patients with hematological malignancies. J Chemother 2006; 18(4): 339–352.

259. Andriula CF, Burdi N, Carella A. CNS cryptococcosis in AIDS: spectrum of MR findings. J Comput Assist Tomogr 1993; 17(3): 438–441.

260. Sun H, Wagener MM, Singh N. Cryptococcosis in solid-organ, hematopoietic stem cell, and tissue transplant recipients: evidence-based evolving trends. Clin Infect Dis 2009, 48(11): 1566–1576.

261. Rofes MA, Huntziek KH, Rhein J et al. The effect of therapeutic lumbar punctures on acute mortality from cryptococcal meningitis. Clin Infect Dis 2014; 59(11): 1607–1614.

262. Gupta RK, Soni N, Kumar S, Khandelwal N. Imaging of central nervous system viral diseases. J Magn Reson Imaging 2012; 35(3): 477–491.

263. Davies NW, Brown LJ, Gonde J et al. Factors influencing PCR detection of viruses in cerebrospinal fluid of patients with suspected CNS infections. J Neurol Neurosurg Psychiatr 2005; 76(1): 82–87.

264. Romee R, Brunstein CG, Weisdorf DJ, Majhail NS. Herpes simplex virus encephalitis after allogeneic transplantation: an instructive case. Bone Marrow Transplant 2010; 45(4): 776–780.

265. Zeiser R, Grüllich C, Bertz H et al. Late cytomegalovirus polyradiculopathy following haploidentical CD34+-selected hematopoietic stem cell transplantation. Bone Marrow Transplant 2004; 33(2): 243–245.

266. Wolf DG, Lurain NS, Zuckerman T et al. Emergence of late cytomegalovirus disease in renal transplant recipients. Transplant Proc 2005; 37(10): 4303–4305.

267. Worth A, Conyers R, Cohen J et al. Pre-emptive rituximab based on viruria and T cell reconstitution: a highly effective strategy for the prevention of Epstein-Barr virus-associated lymphoproliferative disease following stem cell transplantation. Br J Haematol 2011; 155(3): 377–385.

268. Ogata M. Human herpesvirus 6 in hematological malignancies. J Clin Exp Hematol 2009; 49(2): 57–67.

269. Graham A, Studdif M,Nilsson S et al. Varicella-zoster virus (VZV) glycoprotein E is a serological antigen for detection of intrathecal antibodies to VZV in central nervous system infections, without cross-reaction to herpes simplex virus 1. Clin Vaccine Immunol 2011; 18(8): 1336–1342.

270. Casado JL, Corral I, García J et al. Continued declining incidence and improved survival of progressive multifocal leukoencephalopathy in HIV/AIDS patients in the current era. Eur J Clin Microbiol Infect Dis 2014; 33(2): 179–187.

271. Tan CS, Koralnik U. Progressive multifocal leukoencephalopathy and other disorders caused by JC virus: clinical features and pathogenesis. Lancet Neurol 2010; 9(4): 425–437.

272. Pavlović D, Patera AC, Nyberg F et al. Progressive multifocal leukoencephalopathy: current treatment options and future perspectives. Ther Adv Neurol Disord 2015; 8 (9): 255–273.

273. Varzi H, Ruggieri V, Brambilla A et al. Acute mortality from cryptococcal meningitis. Clin Infect Dis 2009; 48(11): 1576–1585.

274. Tan CS, Koralnik IJ. Progressive multifocal leukoencephalopathy and other disorders caused by JC virus: clinical features and pathogenesis. Lancet Neurol 2010; 9(4): 425–437.

275. Sanchez-Quintana A, Breña-Atienza J, Marrero-Santos C, Alvarez-Acosta L. Late relapse of progressive multifocal leukoencephalopathy postalloigenic transplant in a young patient with CLL. BMJ Case Rep 2013 Aug 5 [epub ahead of print], doi: 10.1136/bcr-2013-200213.

276. Balduzzi A, Lucchini G, Hirsch HH et al. Polyomavirus JC-targeted T-cell therapy for progressive multiple leukoencephalopathy in a hematopoietic cell transplantation recipient. Bone Marrow Transplant 2011; 46(7): 987–992.