Current Neurology and Neuroscience Reports (2021) 21: 37
https://doi.org/10.1007/s11910-021-01119-w

INFECTION (K.T. THAKUR, SECTION EDITORS)

Central Nervous System Infections in Immunocompromised Patients

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Accepted: 22 April 2021 / Published online: 26 May 2021

Abstract

Purpose of Review This article reviews current epidemiologic trends, clinical presentations, and diagnostic strategies for central nervous system (CNS) infections in human immunodeficiency virus-negative (HIV) patients immunocompromised by their underlying disease or by receipt of immunosuppressive or immunomodulating therapies. Three patient groups are considered: (1) cancer patients; (2) hematopoietic or solid organ transplantation recipients; and (3) patients with autoimmune or inflammatory conditions requiring therapies that alter the host immune response.

Recent Findings Clinical presentations, associated neuroimaging, and cerebrospinal fluid (CSF) abnormalities differ between immunocompromised and immunocompetent patients. Infections can trigger the emergence of neurotropic antibodies or inflammatory conditions due to treatment with cancer immunotherapies. Unbiased metagenomic assays to identify obscure pathogens help clinicians navigate the increasing range of conditions affecting the growing population of patients with altered immunity.

Summary Awareness of clinical presentations and disease and drug-specific risks is important for early diagnosis and intervention in these often life-threatening infections and their noninfectious mimes.

Keywords Progressive multifocal leukoencephalopathy · Organ transplantation · Herpes viruses · Meningitis · Encephalitis · Disease-modifying therapies

Introduction

Despite appropriate prophylactic regimens and evidence-based antimicrobials, central nervous system (CNS) infections continue to cause significant morbidity and mortality in an increasing range of patients. Multiple new drugs put patients at risk for opportunistic infections such as progressive multifocal leukoencephalopathy, which has numerous imaging and clinical manifestations. In addition to hematopoietic and solid organ transplant recipients and patients with malignancy, others at risk include those with altered immune systems due to treatment for psoriasis; inflammatory bowel disease; rheumatoid arthritis; systemic lupus erythematosus; sarcoidosis; and, of particular concern for neurologists, patients with myasthenia, chronic inflammatory demyelinating polyneuropathy, myositis, aquaporin-4 (AQP4), myelin oligodendrocyte glycoprotein (MOG), and the large population of multiple sclerosis patients, for whom in an era of the pandemic, infection risk and vaccine safety and efficacy become important factors in therapeutic decision making.

This article is part of the Topical Collection on *Infection*

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Diagnostic Approach to Potential CNS Infection

For several reasons, CNS infections in immunocompromised patients present clinical, laboratory, and imaging diagnostic challenges [1••]. These include (1) absence of typical clues to infection such as fever or meningismus, often conspicuously absent in patients receiving corticosteroids which also reduce contrast enhancement on imaging studies; (2) frequent presence of multiple concurrent infections; (3) unusual virulence of pathogens normally of low risk in immunocompetent patients such as West Nile virus, *Babesia*, *Borrelia*, and varicella-zoster virus (VZV) [2•]; (4) occurrence of noninfectious conditions resembling infection, including stroke, seizure, or radiation-related MRI changes, drug-related posterior reversible encephalopathy syndrome (PRES), organ rejection, graft vs. host disease (GVHD), and immune reconstitution inflammatory syndrome (IRIS); (5) novel drug toxicities, especially the evolving spectrum of immune checkpoint

inhibitor (ICI) complications [3,4•]; (6) ambiguous laboratory results due to treatment or disease-related cytopenias that may reduce or eliminate cerebrospinal fluid (CSF) pleocytosis; and (7) development of infection-triggered brain autoimmunity syndromes that could be confused with infection [5, 6].

Situations as complex as those included in this review cannot be safely reduced to algorithmic approaches, but an organized approach to potential CNS infection involves four sets of data. These include consideration of the type of predisposing condition, current epidemiologic risks (from the underlying disease and specific current/past therapies), physical examination leading to syndromic localization, and laboratory and imaging data.

Predisposing Risk Factors for Infections Immunocompromised Patients

Barrier Disruption

Barrier disruption by shunts, monitoring devices, ventricular reservoirs, cranial surgery, central lines or ports, gastrointestinal surgery, urinary catheters, and loss of cutaneous or mucosal integrity, often radiation or chemotherapy induced, predisposes to both bacterial and fungal infections. In these settings, skin-derived organisms such as *Staphylococcus aureus* and *epidermidis*, *Acinetobacter*, and *Propionibacterium acnes* cause bacterial meningitis. Particularly associated with gastrointestinal procedures are *Streptococcus bovis* and *Listeria monocytogenes*. Another gastrointestinal pathogen of growing importance is *Strongyloides stercoralis*.

Neutropenia

Bone marrow infiltration by leukemia, lymphoma or solid tumors, or treatment-induced marrow failure make patients susceptible to all types of bacterial organisms and to invasive fungal infections with *Aspergillus*, *Mucor*, and *Candida*. Sinuses or lungs may be the portal of entry for bacteria and fungi.

B-lymphocyte/Immunoglobulin Deficiency

Predisposing disorders include leukemias, IgA deficiency, splenectomy, multiple myeloma, and lymphoplasmacytic lymphoma. Profound B cell depletion occurs with the increasing use of the monoclonal antibody rituximab for neoplastic or inflammatory diseases. The advent of multiple sclerosis disease-modifying therapies based on cell depletion such as ofatumumab, ocrelizumab, brentuximab, and alemtuzumab produces another population of patients vulnerable to CNS infections.

T-lymphocyte Depletion

A growing list of drugs puts this diverse and numerically largest group of patients at risk for T-lymphocyte/macrophage-deficiency-related infections. These drugs include alemtuzumab, cyclosporine, tacrolimus, sirolimus, mycophenolate, azathioprine, bortezomib, fludarabine, and temozolomide. Disorders producing T cell deficiency as part of the disease process or requiring the above drugs include HIV/AIDS, lymphoreticular neoplasms, organ transplantation, and chronic corticosteroid use. It is in this group of patients that the various herpes viruses become most important as does a spectrum of fungi including *Cryptococcus neoformans*, *Mucoraceae*, *Pseudoallescheria boydii*, *Aspergillus* species, and *Candida* species. Toxoplasmosis is relevant particularly in epidemiologic subgroups with a high seroprevalence of this parasite.

Epidemiologic Trends

Extensive antibiotic use has been accompanied by a selection of resistant organisms. Methicillin-resistant *Staphylococcus aureus* (MRSA) acquired both in the hospital and, increasingly, in the community where over 60% of acquired infections are MRSA assumes a larger role and can be associated with both CNS infections and lethal systemic complications such as necrotizing fasciitis. Community-acquired MRSA infections are associated with recent hospitalization, an invasive medical device, prior colonization, dialysis, or residence in a long-term care facility. Nearly 200 million intravascular devices are sold in the USA each year, and their most common complication is bloodstream infection, ranging from local colonization to bacteremia or candidemia.

Opportunistic fungi have become more frequent lethal pathogens in the past 30 years as nosocomial fungal infection rates have doubled. There is an increased incidence of fungal and other opportunistic diseases among patients who are not terminally ill, and the timing with respect to organ transplantation has changed so that, for example, *Aspergillus* infections occur later post transplantation than they did two decades ago and patients with chronic myelogenous leukemia (CML) now experience increased VZV risk after treatment with imatinib.

There has been a change in the spectrum of organisms causing bacterial and fungal meningitis in cancer patients, with decreased incidence of *Listeria* and dominance of the risk pool for meningitis by patients who have had neurosurgery [7, 8]. The lower incidence of meningitis in transplant patients likely results from trimethoprim/sulfamethoxazole prophylaxis for *Toxoplasma gondii* and *Pneumocystis jiroveci*. However, the increasing use of alemtuzumab results in long-term T cell depletion which reactivates cytomegalovirus (CMV), a situation that also increases the risk of *Listeria*.

Acyclovir prophylaxis has reduced the incidence of herpes viruses and CMV. However, progressive multifocal leukoencephalopathy (PML) is encountered in a broader group of patients, including those who have received rituximab.

Changes in immunosuppression regimens for transplantation patients from corticosteroids, azathioprine, and calcineurin inhibitors to approaches using sirolimus, mycophenolate mofetil, T cell and B cell, and co-stimulatory blockade have reduced *Pneumocystis* infection while increasing activation of CMV, EBV, and HIV [9]. Late infections due to cellular depletion favor CMV and John Cunningham (JC) viruses as well as fungal conditions, with even later development of secondary malignant conditions.

In primary and metastatic brain tumor patients, the evolving strategies of concurrent chemotherapy, immunotherapy, chimeric antigen receptor technology (CAR T), and proton radiation regimens have been associated with new neurological toxicities [10•]. It is also important to recognize new therapy-related ambiguous MRI abnormalities including chemoradiation-related pseudoprogression.

Clinical Syndromes on Physical Examination

Rarely does a specific localization pinpoints a unique pathogen as most organisms can infect multiple sites and noninfectious causes can target certain CNS areas preferentially. Nevertheless, an important diagnostic step for any neurologic consultant is the traditional localization of the patient's problem to a broad category of neuroanatomical presentation. Generally, the process can be conceived as either meningitis/meningoencephalitis pattern or one with focal signs, suggesting a brain parenchymal process. The former group would include entities such as bacterial or fungal meningitis, notably *Cryptococcus* [11]. The latter group can be further subdivided into presentations consistent with a focal mass lesion, leukoencephalopathy (PML, among other possibilities), stroke-like vascular distribution, and more clinically and radiographically restricted processes such as viral tropisms producing limbic encephalitis (human herpes virus 6 [HHV6], herpes simplex virus [HSV], VZV) or movement disorders (West Nile) and brainstem syndromes (*Listeria*, osmotic demyelination, Wernicke encephalopathy, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids [CLIPPERS]). Focal deficits due to macroabscesses suggest *Nocardia or Aspergillus* species, the latter of which can present with hemorrhagic infarction [12].

Stroke-like vascular syndromes can suggest bacterial fungal or nonbacterial thrombotic endocarditis, VZV, or intravascular lymphoma. At times, the concurrence of two CNS patterns gives a hint as to the underlying pathogen. For example, cryptococcal meningitis is characterized by headache, cranial nerve palsies, and lethargy, all manifestations of raised intracranial pressure (ICP) due to obstruction of CSF outflow. The increased ICP can worsen after treatment as lysis of yeast further obstructs CSF flow and serial lumbar punctures may be necessary [13••]. MRI may reveal evidence of lacunar infarction in up to a quarter of such patients, and in the appropriate clinical setting, the combination of raised ICP and infarction raises suspicion for cryptococcal meningitis; the mechanism is thought to be a vasculitis resulting in ischemia [14, 15].

Organisms targeting the spinal cord include viral infections such as West Nile virus (WNV), Powassan virus, enteroviruses A71 and D68, poliovirus, CMV, human herpes virus 7, and VZV. Human T cell lymphotropic virus type 1 transmitted after living donor live transplantation has been reported [16]. Infectious epidural cord compression is usually of bacterial origin. Holocord edema can be caused by viral infections and also by chemotherapy (methotrexate), carcinomatous meningitis, radiation-related injury, and autoimmune/paraneoplastic processes such as aquaporin 4 and MOG-related conditions.

Extra-CNS infection sites may provide clues to pathogens or offer biopsy sites. Examination of the eyes skin, sinuses, and lungs which are the main entry portals for many pathogens can help with the diagnosis of cryptococcosis, aspergillosis, or mycobacterial infections. An ocular examination is useful for the diagnosis of primary CNS lymphoma, VZV, or CMV retinitis as well as to assess for GVHD in the appropriate circumstances. A skin biopsy may be useful for confirmation of *Cryptococcus*, *Aspergillus*, VZV, HSV, or EBV-associated intravascular lymphoma.

Laboratory and Imaging Considerations

Because of the possibility of space-occupying lesions and the frequent dearth of signs of elevated intracranial pressure, it is the author's practice to obtain at least a head CT and preferably an MRI scan prior to lumbar puncture in all immunocompromised patients. The use of MRI contrast should be considered if the patient's renal function permits. There are numerous pitfalls in the interpretation of CSF and MRI scans in immunocompromised patients. These include

a) reduced or absent contrast enhancement after the use of corticosteroids or vascular endothelial growth factor (VEGF) inhibitors such as bevacizumab;
b) inability to give gadolinium compounds safely due to renal insufficiency (glomerular filtration rate less than 30 mL/min);
c) diffuse meningeal enhancement and fluid-attenuated inversion recovery (FLAIR) abnormalities after multiple seizures;

d) diffuse dural enhancement mimicking metastatic or granulomatous disease due to low ICP after lumbar puncture;
e) the broad differential diagnosis of ring-enhancing lesions that includes infection and also tumor recurrence, radiation necrosis, and pseudoprogression;
f) the variable appearance of PML including location and contrast enhancement (see "Discussion"); and
g) the atypical appearance of HSV in immunocompromised patients [17].

Cerebrospinal fluid (CSF) should be cultured for bacterial and fungal pathogens, but some organisms require lengthy incubation periods. Meningitis encephalitis panels provide a convenient broad screen for multiple organisms. Polymerase chain reaction (PCR) tests are useful in the acute phase. The choice of test depends on how acute the presentation is so that PCR for various viral infections is appropriately supplanted by serum:CSF IgG antibody ratios when the patient has a more chronic (> 7–10 days) presentation. Metagenomic next-generation sequencing (mNGS), available at a few centers, is an increasingly rapid and relatively low-cost means of screening CSF for a broad range of human pathogens when selective serology and CSF microbiological testing is unhelpful. In a 2017 series from Michael Wilson's laboratory at UCSF, unusual causes of encephalitis such as *Balamuthia mandrillaris* were identified. In all, 35 CNS infections were identified in 151 patients, more than one third of which were not revealed by conventional testing. mNGS may be particularly helpful for exclusion of CNS infection in an immunosuppressed patient when a noninfectious cause such as an autoimmune condition seems likely [18]. This method eventually may replace many single-agent laboratory assays [19••].

Noninfectious Conditions Mimicking or Co-Occurring with CNS Infections

This section describes several syndromes that may raise suspicion of CNS infection and have other mechanisms and may indeed need to be treated with immune suppression rather than antimicrobial therapy. Because neuroimaging can result in an ambiguous picture, it is important to be aware of infectious mimes.

The first such condition is autoimmune encephalitis and its known relation to antecedent systemic and also CNS infection. An antecedent viral illness occurs in up to 70% of patients found to have NMDA receptor encephalitis. Anti-NMDA receptor encephalitis is the most commonly recognized cause of antibody-mediated autoimmune encephalitis and may in some cases be triggered by herpes simplex virus infection or cranial irradiation [20]. While it would seem counterintuitive that an autoimmune condition could develop during immunosuppression, there is precedent, for example, in patients post-allogeneic hematopoietic stem cell transplantation (HSCT) with GVHD who have a tendency to develop polymyositis, myasthenia gravis, and Guillain–Barré syndrome. Having a concurrent viral infection such as EBV could increase blood–brain barrier permeability. Complex immunologic interactions contribute to the development of this nonparaneoplastic anti-NMDAR. Thus, in patients on immunomodulatory therapy, the diagnosis of an autoimmune antibody-mediated condition should be considered in an infectious differential when the clinical picture is suggestive of such a syndrome [21]. Other conditions such as Rasmussen's encephalitis (RE) and febrile infection-related epilepsy syndrome (FIRES) have also been posited to be autoimmune conditions triggered by infectious agents. Finally, ICIs have resulted in the appearance of paraneoplastic antibodies and their associated syndromes.

Posterior reversible encephalopathy syndrome (PRES) was described 25 years ago. PRES is a form of vasogenic edema resulting from hypertension or from endothelial dysfunction due to numerous drugs including many chemotherapy agents and the calcineurin inhibitors used in transplantation. There are typically posterior predominant supratentorial areas of white matter vasogenic edema but many variations including posterior fossa, spinal cord, and "central" variants occur [22]. PRES should resolve with control of blood pressure and withdrawal of the offending agent.

Immune reconstitution inflammatory syndrome (IRIS) is better recognized in the HIV population, and this dysfunctional, exuberant host inflammatory response can be triggered by rapid host immune recovery in non-HIV patient groups as well [23]. New or worsening clinical and radiographic signs appear that cannot be explained by a newly acquired infection. CSF elevated pressure and pleocytosis may be present, further complicating differential diagnosis. Examples in the non-HHIV population include cryptococcal IRIS in the setting of solid organ transplantation (SOT) patients or following alemtuzumab for lymphoma, TB after discontinuation of infliximab, a relapsing-remitting MS-like illness in transplant patients with GVHD, and CMV retinitis after withdrawal of intense immunosuppression following organ transplantation [24].

Demyelinating syndromes can be caused by several groups of drugs causing resultant confusion with infection. Acute disseminated encephalomyelitis (ADEM) and other demyelinating syndromes including inflammatory pseudotumor can be provoked by TNF-α inhibitors [25•]. Recently, immune checkpoint inhibitors have been reported to cause similar unmasking of demyelinating disease. In the US FDA Adverse Event Reporting System (FAERS), 14 cases of MS in patients exposed to pembrolizumab, atezolizumab, nivolumab, ipilimumab, avelumab, or durvalumab in the 2 years prior to their FDA approval. The median time of onset after ICI therapy was 29 days, and several cases were extremely severe [26].

Considerations for Specific Patient Populations

Cancer Patients

CNS infections occur in a relatively small subset of cancer patients. Patients with hematopoietic stem cell transplantation (HSCT) are a particularly high-risk group, while patients with leukemia or lymphoma represent more than a quarter of those with CNS infections, and 16% of CNS infections in cancer patients occur among those who have primary CNS tumors who have had neurosurgical procedures. With the increased use of dose intense regimens including potent immunosuppressive purine analogs such as fludarabine, pentostatin, and cladribine as well as anti-T and anti-B cell antibodies such as alemtuzumab and rituximab, the number of at-risk patients with hematologic malignancies who did not have transplants nearly equals those receiving allogeneic stem cell transplants.

With the "immunorevolution" of cancer therapy in the past 5 years, neurologists have been confronted with an increasing array of potentially confusing syndromes. Immune checkpoint inhibitors (ICIs) such as anti-CTLA-4 agents including ipilimumab and PD-1 or PD-L1 inhibitors such as nivolumab, pembrolizumab, atezolizumab, and many other new agents have vastly improved the prognosis for patients with melanoma and nonsmall cell lung cancer including those with CNS metastases. CNS complications of the ICIs can include hypophysitis, acute encephalitis, cerebellitis, and demyelinating syndromes [27••]. In the presence of possible immune-mediated encephalitis, the author recommends the following procedures:

a) measure pituitary axis to rule out hypophysitis and other endocrinopathies;
b) MRI to rule out stroke or brain or leptomeningeal metastases;
c) lumbar puncture to exclude infection or leptomeningeal metastases;
d) EEG monitoring, possibly with long-term monitoring (LTM) to rule out nonconvulsive status epilepticus; and
e) blood and CSF paraneoplastic panels.

However, one should not wait for the antibody results before discontinuing ICI therapy and starting high-dose corticosteroids.

Transplant Recipients

Transplant recipients typically follow immunosuppressive regimens that include mycophenolate, tacrolimus or equivalent drugs, and corticosteroids. Mycophenolate impairs lymphocyte function via inhibition of inosine monophosphate dehydrogenase, resulting in decreased purine synthesis which in turn inhibits guanosine nucleotide synthesis on which T and B lymphocytes depend. Tacrolimus inhibits T cell activation by inhibiting calcineurin phosphatase activity.

Transplant recipients are at risk for transmission from infected donors, notably in recent years for West Nile Virus and rabies. In one series, confirmed CNS infection occurred in 12 donors, six of whom transmitted infection to 10 of 15 exposed recipients with five recipient deaths. Pathogens included *Balamuthia mandrillaris*, *Cryptococcus neoformans*, lymphocytic choriomeningitis virus, and West Nile virus. The listed cause of death for the donors included stroke, anoxia, acute disseminated encephalomyelitis, and meningoencephalitis (BLUMBERG). The authors warned that careful clinical assessment of donors combined with a high index of suspicion for ambiguous or misleading findings associated with CNS infection can reduce donor-derived infection with CNS pathogens [28].

Specific CNS infections tend to occur at predictable time intervals from transplantation. Almost 70% of clinically significant neurologic complications occurred within the first 200 days after the procedure [29]. Most opportunistic infections occur 2–6 months post transplantation, and this is when pathogens such as VZV, CMV, and *Cryptococcus* are prevalent. In the period from 6 months to many years after transplantation, opportunistic infections such as PML remain a risk. A detailed table of infections and infectious mimes by the interval from the transplantation procedure can be found in Pruitt [30••].

Herpes viruses remain a problem throughout the post-transplantation period both in hematopoietic cell transplantation (HCT) and in SOT. Among the protean manifestations of this virus are strokes, transverse myelitis, meningoencephalitis, and retinitis [31, 32]. A distinct infection due to human herpes virus 6 subtype b (HHV6) occurs at the time of engraftment in HCT (about 3 weeks post infusion). Seizures and an MRI pattern of limbic encephalitis are seen [33].

Progressive multifocal leukoencephalopathy is fittingly discussed in this section devoted to transplants and also appropriate that this topic comes just before consideration of another group of people whose disease and therapies make them susceptible to this oligodendrocyte-lysing polyoma virus. In the nearly half century since its causal agent, the John Cunningham (JC) virus was identified; PCR of CSF has simplified diagnosis. Clinical and radiographic features of PML are quite variable; a recently described helpful diagnostic feature is a rim of diffusion restriction in the advancing border of these white matter lesions and a report of susceptibility-weighted cortical abnormalities before the development of white matter lesions with concomitant clinical deterioration [34]. Multiple groups of patients are at risk for PML (see Table 1 for drugs associated with PML), and no definitive therapy has been developed, though a small series suggested that 5 of 8 patients treated with pembrolizumab had a somewhat durable response [35••].

Table 1 Drugs associated with risk of specific CNS infections

Drug	Molecular target	Indication	CNS infections
I. Drugs approved for neurological conditions			
Alemtuzumab	CD52	Multiple sclerosis	VZV, HSV, TB, PML, CMV, *Listeria*, *Nocardia*
Dimethyl fumarate	Nrf2 upregulator	Multiple sclerosis	PML, VZV
Eculizumab		AQP4, myasthenia gravis	*Neisseria meningitidis*
Fingolimod	Sphingosine-1-phosphate inhibitor	Multiple sclerosis	VZV, HSV, PML, *Cryptococcus*, *Listeria*
Natalizumab	α4 integrin inhibitor	Multiple sclerosis	PML VZV, HSV
Ocrelizumab	CD20	Multiple sclerosis	VZV, HSV, PML*
Teriflunomide	Pyrimidine synthetase inhibitor	Multiple sclerosis	PML, TB
Corticosteroids (prednisone, methylprednisolone, dexamethasone)	Anti-inflammatory, T cell inhibition	Multiple indications	PML, VZV, PJP, *Candida*
II. Drugs used off label for neurological conditions			
Azathioprine	Antimetabolite, purine analog	Myasthenia gravis, CIDP, AQP4, MS, polymyositis, vasculitis, neurosarcoidosis	PML, CMV, EBV-associated PCNSL
Cyclophosphamide	Alkylating agent	MS, MMN, neurosarcoidosis, vasculitis, lupus, inflammatory myopathies, autoimmune paraneoplastic syndromes	PML, sepsis, bacterial infections (urine, lung)
Ibrutinib	Bruton's tyrosine kinase inhibitor	PCNSL	*Aspergillus*, PML
Infliximab	TNF-alpha inhibitor	Neurosarcoidosis	VZV, TB, PML, demyelinating lesions ➔ MS
Methotrexate	Folate analog inhibitor	Sarcoidosis, PCNSL, lupus, polymyositis	Toxoplasmosis, EBV-associated lymphoproliferative disorder
Mycophenolate mofetil	Inosine 5′-monophosphate dehydrogenase inhibitor	Myasthenia gravis, MS, AQP4, CIDP, neurosarcoidosis	PML, PCNSL
Rituximab**	CD20	MS, AQP4, MMN, myositis, myasthenia gravis, autoimmune encephalitis, PCNSL	Toxoplasmosis, enterovirus, *Babesia*, WNV, CMV, VZV, *Cryptococcus*, PJP, Powassan virus, PML
III. Drugs associated with CNS infections with no primary neurological indication			
Adalimumab (also certolizumab, etanercept)	TNF-alpha inhibitor	IBD, psoriasis, RA, JRA, ankylosing spondylitis	PML
Brentuximab	CD30	T cell lymphoma, Hodgkin lymphoma	PML
Cyclosporine/tacrolimus	Calcineurin inhibitor	transplantation	
Fludarabine	Antimetabolite, purine analog	ALL, AML, CLL, HCT	PML, VZV, HSV, *Listeria*, *Cryptococcus*
Leflunomide	Pyrimidine synthase inhibitor	RA, psoriatic arthritis	PML, TB
Ruxolitinib	Janus kinase inhibitor	GVHD	PML, toxoplasmosis

*PML associated with ocrelizumab to date only seen in patients previously on natalizumab or dimethyl fumarate

**Rituximab associated with reactivation of hepatitis B virus and the unusual severity of infections with *Babesia* and WNV

ALL, acute lymphoblastic leukemia; *AML*, acute myelocytic leukemia; *AQP4*, aquaporin-4 disease (previously, neuromyelitis optica); *CIDP*, chronic inflammatory demyelinating polyneuropathy; *CLL*, chronic lymphocytic leukemia; *CMV*, cytomegalovirus; *EBV*, Epstein–Barr virus; *GVHD*, graft vs. host disease; *HCT*, hematopoietic cell transplantation; *HSV*, herpes simplex virus; *IBD*, inflammatory bowel disease; *JRA*, juvenile rheumatoid arthritis; *MMN*, multifocal motor neuropathy; *PCNSL*, primary *CNS*, lymphoma; *PJP*, *Pneumocystis jirovecii* pneumonia; *PML*, progressive multifocal leukoencephalopathy; *RA*, rheumatoid arthritis; *TB*, *Mycobacterium tuberculosis*; *TNF*, tumor necrosis factor; *VZV*, varicella-zoster virus; *WNV*, West Nile virus

Patients with Altered Immunity due to Treatment of Various Inflammatory Conditions

An ever-increasing population of patients is treated with drugs that alter the immune system. Some of these therapies are also used for neoplasia and have found a place in the treatment of non-neoplastic indications including rheumatologic, dermatologic, ocular, and inflammatory gastrointestinal conditions. Effective treatment of many neurologic disorders requires dampening of the immune response to varying degrees. Therapies that broadly suppress the immune system, including cyclophosphamide, azathioprine, mycophenolate mofetil, cyclosporine, methotrexate, mitoxantrone, and tacrolimus, are classified as "immunosuppressive" drugs. Drugs that are immunomodulatory induce, enhance, or suppress a specific immune response, targeting one or a few components of the immune system. Such drugs predispose patients to specific pathogens [36].

Patients with MS are at a generally increased risk of infections such as respiratory illnesses and UTIs, and this risk varies by degree of disability and by treatment. The rate of infections (both systemic and CNS) is lowest with interferon beta and glatiramer acetate; among newer treatments, off-label use of rituximab was associated with the highest rate of serious infections. The different risk profiles should inform the risk–benefit assessment, particularly in the current pandemic period [37••].

Recent studies address the possibility of mitigating such infection risk by altering the frequency of administration of B cell, depleting drugs beyond, for example, the current semi-annual administration of ocrelizumab or of decreasing regular rituximab infusion to half its usual current dose [38, 39].

While the older platform therapies such as glatiramer acetate and the interferons are not associated with significant CNS infection risk, a rapidly increasing number of multiple sclerosis patients receiving disease-modifying therapy that increases the risk for a variety of CNS infections. The most notable example is PML risk with natalizumab, but many currently used MS therapies also increase the risk of VZV and TB. Table 1 shows drugs associated with the risk of specific CNS infections, a list which necessarily is incomplete as new drug infection associations appear literally monthly. The table highlights drugs approved for neurologic conditions; those drugs used off label for neurologic conditions and those medications associated with elevated CNS infection risk that neurologists may encounter in consultation, though the indication for the responsible agent was a non-neurologic condition.

Several immunomodulatory drugs deserve special mention here. Three months after its initial approval in 2005, natalizumab was associated with three cases of PML. Over 800 cases have now been reported worldwide with an incidence of at least 1 per 1000 patients who are JCV positive and who have received the drug for more than 1 year [40]. No therapy except cessation of the drug has been approved for natalizumab-associated PML. Reported unproved or challenged empirical treatment attempts include plasma exchange (PLEX) to expedite the elimination of natalizumab, mirtazapine as a potential blocker of virus entry into cells, and mefloquine for its possible anti-JCV proliferative properties. Filgrastim (also known as a granulocyte-colony stimulating factor [G-CSF]) promotes immune system restoration after intensive immunosuppression from chemotherapy. Recent promising data for the use of filgrastim for natalizumab-related PML have been reported in a small number of patients [41]. Natalizumab has been associated with other CNS infections and, as is the case for many patients with MS, presentation of a CNS infection initially may be confused with a demyelinating disease relapse [42, 43].

Some cases of PML have been reported with fingolimod which also has been associated with VZV, disseminated HSV, and disseminated cryptococcosis [44]. VZV status should be checked before therapy and vaccination completed before initiation of therapy with regular CD4 lymphocyte count monitoring. Ocrelizumab was introduced in 2017. Though it is closely related to rituximab, cases of PML thus far in MS patients have been reported only in those previously receiving natalizumab, and thus, it is thought that this was a preexisting infection more likely due to natalizumab. Nevertheless, regular monitoring of JCV titers is recommended for ocrelizumab-treated patients [45].

Vaccine-Preventable Infections

Revision of vaccination guidelines is an evolving process, and clinicians must be aware of specific vaccination requirements before prescribing immune system-altering medications. For example, the introduction of eculizumab mandates prior vaccination for *Neisseria meningitidis*, and it is advisable to vaccinate against VZV for several immune-modulating therapies for MS. See Table 2 for vaccine safety guidelines and recommendations [46]. Based on this author's assessment of current theoretical knowledge about mRNA-based COVID 19 vaccines, most immunocompromised patients should be advised to accept COVID 19 vaccination when it is offered. Ongoing studies seek to elucidate appropriate intervals for maximum vaccine response in immune-compromised patients [47, 48••].

Conclusion

CNS infections remain a source of morbidity and mortality for many groups of patients receiving chemotherapy for tumors, immunosuppression for transplantation, and immunomodulating therapies for a variety of inflammatory conditions and

Table 2 Vaccine safety recommendations for immunocompromised patients*

Inactivated or recombinant vaccines (generally safe on any DMT)	Live/attenuated vaccines mRNA vaccines† (Do not use while on [risk unknown, but specific DMTs as previously mentioned] theoretically safe)
Inactivated influenza vaccine	Live nasal spray influenza vaccine
Hepatitis A	Yellow fever
Hepatitis B	Measles, mumps, rubella (MMR)
Human papilloma virus (HPV)	Older varicella-zoster vaccine**
DTaP	Cholera
TD	Adenovirus
Inactivated polio vaccine	
Meningococcal vaccine	
Pneumococcal vaccine	
Rabies	
Varicella-zoster (Shingrix)**	

Table modified from Grebenciucova and Pruitt [45]

*Antibody response may be attenuated for patients on some disease-modifying therapies: two influenza vaccinations may be recommended

**Varicella-zoster required prior to alemtuzumab or fingolimod treatment and recommended, if possible, before ocrelizumab

†Timing of vaccination with respect to ocrelizumab infusion should be optimized to afford the best chance of a robust immune response (2nd dose $\geq$ 2 weeks before next infusion)

autoimmune conditions. Despite many confounding variables that make rapid identification of specific pathogens and exclusion of noninfectious causes difficult, recognition of demographic risk factors, knowledge of specific medication risks, accurate delineation of anatomic syndromes, and judicious choice of diagnostic imaging and laboratory tests help narrow the range of possibilities. Attention to local environmental and nosocomial patterns, adherence to antimicrobial prophylactic strategies and vaccination guidelines, and frequent interdisciplinary consultation will improve outcomes for these complex patients.

Declarations

Conflict of Interest The author declares that she has no conflict of interest.

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

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1.•• Sonneville R, Magalhaesa E, Meyfroidt G. Central nervous system infections in immunocompromised patients. Curr Opin Crit Care. 2017;23(2):128–33 **Excellent overview of infections in groups including HIV patients**.

2.• Mukerji SS, Ard K, Schaefer PW, Branda JA. Case 32-2020: a 63-year-old man with confusion, fatigue, and garbled speech. N Engl J Med. 2020;383:1578–86 **An interesting CPC discussion of novel pathogens in the context of a man who developed Borrelia miyamotoi after receipt of prednisone, cyclosporine, and 21 months of rituximab for membranous nephropathy.**

3. Stuby J, Herren T, Guidoc SN, Claudiad P, Alain R. Immune checkpoint inhibitor therapy-associated encephalitis: a case series and review of the literature. Swiss Med Wkly. 2020;150:w20377

Published 23 November 2020. https://doi.org/10.4414/smw.2020.20377.

4.• Sechi E, Markovic SN, McKeon A, Duby D, et al. Neurologic autoimmunity and immune checkpoint inhibitors autoantibody profiles and outcomes. Neurology. 2020;95:e2442–52. https://doi.org/10.1212/WNL.0000000000001063 **Discusses the newly recognized phenomena of both central and peripheral neurologic complications of ICIs and the emergence of some of the classic paraneoplastic syndromes in the presence of ICIs**.

5. Armangue T, Leypoldt F, Malaga I, et al. Herpes simplex virus encephalitis is a trigger of brain autoimmunity. Ann Neurol. 2014;75(2):317–23.

6. Venkatesan A, Benavides DR. Autoimmune encephalitis and its relation to infection. Curr Neuro Neurosci Rep. 2015;15(3):3. https://doi.org/10.1007/s1910-0150-529-1.

7. Safdieh JE, Mead PA, Sepkowitz KA, et al. Bacterial and fungal meningitis in patients with cancer. Neurology. 2008;70912:943–7.

8. Costerus JM, Brouwer MC, Van der End A, van de Beek D. Community-acquired bacterial meningitis in aduts with cancer or a history of cancer. Neurology. 2016;86(9):860–6. https://doi.org/10.1212/WNL.0000000000002315.

9. Basic-Jukic N, Juric I, Furic-Cunko V, Kastelani Z. Central nervous system infections in renal transplant recipients. Transpl Infect Dis. 2020;22:e13341.

10.• Perrinjaqueta C, Desbaillets N, Hottinger AF. Neurotoxicity associated with cancer immunotherapy: immune checkpoint inhibitors and chimeric antigen receptor T-cell therapy. Cur Op Neurol. 2019;32(3):500–10 **Well-written overall review.**

11. Williamson PR, Jarvis JN, Panackal AA, Fisher MC et al. Cryptococcal meningitis: epidemiology, immunology, diagnosis and therapy. Nat Rev Neurol 2017;13 https://doi.org/10.1038/nrneurol.2016.167. Published online 25 Nov 2016

12. Coussement J, Lebeaux D, Rouzaud C, Lortholary O. *Nocardia* infections in solid organ and hematopoietic stem cell transplant recipients. Curr Opin Infect Dis. 2017;30:545–51.

13.•• Anderson JD, Ho VT, Wright KT, Levy BD, Lascalzo J. Parroting lymphoma. N Engl J Med. 2020;383:1378–81 **This is a nice clinical problem-solving case in a 48-year-old man heavily treated for EBV-positive diffuse large B cell lymphoma who presents with fever and headache.**

14. Mishra AK, Arvind VH, Muliyil D, Kuriakose CK, George AA, Karuppusami R, et al. Cerebrovascular injury in cryptococcal meningitis. Int J Stroke. 2018;13:57–65.

15. Vela-Duarte D, Nyberg E, Silau S, et al. Lacunar stroke in cryptococcal meningitis: clinical and radiographic features. J Stroke Cerebrovasc Dis. 2019;28:1767–72.

16. Soyama A, Eguchi S, Takatsuki M, Ichikawa T, Moriuchi M, Moriuchi H, et al. Human T-cell leukemia virus type 1-associated myelopathy following living donor liver transplantation. Liver Transpl. 2008;14(5):647–50.

17. Tan IL, McArthur JC, Venkatesan A, Nath A. Atypical manifestations and poor outcome of herpes simplex encephalitis in the immunocompromised. Neurology. 2012;79(21):2125–32.

18. Wilson MR, O'Donovan BD, Gelfand JM, Sample HA, Chow FC, Betjemann JP, et al. Chronic meningitis investigated via metagenomic next-generation sequencing. JAMA Neurol. 2018;75:947–55. https://doi.org/10.1001/jamaneurol.2018.0463.

19.•• Wilson MR, Sample HA, Zorn KC, Arevalo S, Yu G, et al. Clinical metagenomic sequencing for diagnosis of meningitis and encephalitis. N Engl J Med. 2019;380:2327–40. **This UCSF laboratory has identified unusual pathogens in undiagnosed meningitis case by finding non-human nucleic acid in CSF specimens.**

20. Ng S, Le Corre M, Aloy E, Gras-Combe G, Duffau H, Boetto J. Herpes simplex encephalitis shortly after surgery for secondary glioblastoma: a case report and review of the literature. Sep. 2019;129:13–7. https://doi.org/10.1016/j.wneu.2019.05.173.

21. Zhao CZ, Erickson J, Dalmau J. Clinical reasoning: agitation and psychosis in a patient after renal transplantation. Neurology. 79: e41–4.

22. Fugate JE, Rabinstein AA. Posterior reversible encephalopathy syndrome: clinical and radiological manifestations pathophysiology, and outstanding questions. Lancet Neurol. 2015;14(9):914–25.

23. Sueki H, Mizukawa Y, Aoyama Y. Immune reconstitution inflammatory syndrome in non-HIV immunosuppressed patients. J Derm. 2018;45:3–9.

24. Sun HY, Singh N. Opportunistic-infection immune reconstitution inflammatory syndrome in transplant recipients. Clin Infect Dis. 2011;53(2):168–76.

25.• Kunchok A, Aksamit AJ Jr, Davis JM III, et al. Association between tumor necrosis factor inhibitor exposure and inflammatory central nervous system events. Published online May 18, 2020. JAMA Neurol. https://doi.org/10.1001/jamaneurol.2020.1162.11. **An important series that highlights risk of demyelinating events with TNF-α inhibitors exposure.**

26. Garcia CR, Jayswal R, Adams V, Anthony LB, Villano JL. Multiple sclerosis outcomes after cancer immunotherapy. Clin Transl Oncol. 2019;21(10):1336–42. https://doi.org/10.1007/s12094-019-02060-8.

27.•• Larkin J, Chmielowski B, Lado CD, Hodi S, et al. Neurologic serious adverse events associated with nivolumab plus ipilimumab or nivolumab alone in advanced melanoma, including a case series of encephalitis. Oncologist. 2017;22:709–18 **The series discusses recently described syndromes and develops diagnostic strategies to distinguish autoimmune from infectious encephalitis.**

28. Kaul DR, Covington S, Taranato S, Green M, et al. Solid organ transplant donors with central nervous system infection. Transplantation. 2014;98:666Y670.

29. Cohen BA, Stosor V. Opportunistic infections of the central nervous system in the transplant patient. Curr Neurol Neursci Rep. 2013;13(9):376.

30.•• Pruitt AA. Infections complicating immunosuppression and transplantation. Continuum. 2018;24(5):1370–96 **Comprehensive review with tables and case studies relevant to the subject of this review.**

31. Baldwin KJ, Cummings CL. Herpesvirus infections of the nervous system. Continuum. 2018;24(5):1349–69.

32. Pawlitzki M, Teuber J, Campe C, Wagner M, Schuart C, Paul F, et al. VZV-associated acute retinal necrosis in a patient with MS treated with natalizumab. Neurol Neuroimmunol Neuroinflamm. 2018;5:e475. https://doi.org/10.1212/NXI.0000000000000475.

33. Bhanushali MJ, Kranick SM, Freeman AF, Cuellar-Rodriguez JM, Battiwalla M, Gea-Banacloche JC, et al. Human herpes 6 virus encephalitis complicating allogeneic hematopoietic stem cell transplantation. Neurology. 2013;80(16):1494–500.

34. Ueno H , Kikumto M, Takebayashi Y, Ishibashi H, et al. Pomalidomide-associated PML in multiple myeloma: cortical susceptibility-weighted imaging hypointense findings prior to clinical deterioration 2020;26(3):452-455. https://doi.org/10.1007/s13365-020-00845-0

35.•• Cortese I, Muranski P, Enose-Akahata Y, Ha S-K, Smith B. Pembrolizumab treatment for progressive multifocal leukoencephalopathy. NEJM. 2019;380:1597–605 **Since this publication, there have been case reports and a small series of similar responses of PML to this PD-1 inhibitor.**

36. Williamson EM, Berger JF. Central nervous system infections with immunomodulatory therapies. Continuum. 2015;21(6):1577–98.

37.•• Luna G, Alping P, Burman J, Fink K, et al. Infection risks among patients with multiple sclerosis treated with fingolimod, natalizumab, rituximab, and injectable therapies. JAMA Neurol. 2020;77(2):184–91 **This study based on a nationwide register-based cohort in Sweden found that compared with interferon beta and glatiramer, the off-label use of rituximab was**

associated with the highest risk of serious infections (both systemic and CNS). More patients on natalizumab and fingolimod received herpes antivirals. Subclinical carryover of natalizumab explained the two cases of PML in patients with fingolimod and rituximab, respectively.

38. Disanto G, Ripellino P, Riccitelli GC, et al. De-escalating rituximab dose results in stability of clinical, radiological, and serum neurofilament levels in multiple sclerosis. Mult Scler. 2020. https://doi.org/10.1177/1352458520952036. Online ahead of print.
39. Chisari CG, Grimaldi LM, Salemi G, Ragonese P, Iaffaldano P, Bonavita S, et al. Clinical effectiveness of different natalizumab interval dosing schedules in a large Italian population of patients with multiple sclerosis. J Neurol Neurosurg Psychiatry. 2020;91:1297–303.
40. Berger JR. Classifying PML risk with disease modifying therapies. Mult Scler Rel Dis. 2017;12:59–63.
41. Stefoski D, Balabanov R, Waheed R, Ko M, et al. Treatment of natalizumab-associated PML with filgrastim. Ann Clin Transl Neuro. 2019;6(5):923–31.
42. Ruggieri S, Logoteta A, Martini G, Bozzao A, DeGiglio L. Listeria monocytogenes–induced rhombencephalitis in a patient with multiple sclerosis treated with dimethyl fumarate. JAMA Neurol. 2018;75:762–3.
43. Thomas K, Schultheiss T, Ziemssen T. Neuroborreliosis during natalizumab treatment in multiple sclerosis. Neurology. 2013;81:1012–3.
44. Arvin AM, Wolinsky JS, Kappos L, Morris MI, Reder AT, Tornatore C, et al. Varicella-zoster virus infections in patients treated with fingolimod: risk assessment and consensus recommendations for management. JAMA Neurol. 2015;72(1):31–9.
45. Grebenciucova E, Pruitt A. Infections in patients receiving multiple sclerosis disease-modifying therapies. Curr Neurol Neurosci Rep. 2017;17:88.
46. Center for Disease Control and Prevention (CDC): recommended adult immunization schedule, United States. 2017.
47. Bar-Or A, Calkwood JC, Chognot C, et al. Effect of ocrelizumab on vaccine responses in patients with multiple sclerosis: the VELOCE study. Neurology. 2020;95(14):1999–2008.
48.•• Farez MF, Correale J, Armstrong MG, Rae-Grant A, et al. Practice guideline update summary: vaccine-preventable infections and immunization in multiple sclerosis. Neurology. 2019;93:584–94. https://doi.org/10.1212/WNL0000000000008157 **An important reference for practicing clinicians. It is hard to give definitive advice about mRNA COVID-19 vaccinations at the time of this writing (see text).**