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Opportunistic Infections of the Central Nervous System in the Transplant Patient

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Abstract Therapeutic advances in transplantation medicine have resulted in ever expanding patient populations that receive organ or stem cell transplantation. Modern potent immunomodulatory therapies have resulted in improvements in allograft and patient survival, but, consequently, as a result of the immunosuppressive state, transplant recipients are highly vulnerable to infection, including those that affect the central nervous system (CNS). CNS infections present a diagnostic and therapeutic challenge for clinicians involved in the care of the transplant patient, with a propensity to result in profound morbidity and often high mortality in this patient population. Here, we review major opportunistic pathogens of the CNS seen in transplant patients, highlighting distinguishing epidemiologic and clinical features.

Keywords Nervous system infection · Opportunistic infection · Organ transplantation · Stem cell transplantation · Meningoencephalitis · Meningitis · Encephalitis · Cerebritis · Brain abscess · Myelitis · Progressive multifocal leukoencephalopathy · Cytomegalovirus · Epstein–Barr virus · Herpes simplex virus · Human herpesvirus-6 · Human herpesvirus-7 · Varicella-zoster virus · JC virus · *Toxoplasma gondii* · *Aspergillus* · *Cryptococcus* · Mucormycosis · *Listeria monocytogenes* · *Nocardia* · *Mycobacterium tuberculosis*

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Introduction

Opportunistic infections (OI) of the central nervous system (CNS) complicating transplantation present significant diagnostic and therapeutic challenges. Immunosuppression strategies aimed at preventing and treating rejection in solid organ transplantation (SOT) and graft versus host disease (GVHD) in stem cell transplantation (SCT) leave transplant recipients susceptible to OI, which may occur owing to reactivation of latent organisms residing in the host, or may be acquired as a result of exposures to the environment or transmission from donor organs. The incidence of CNS infection varies according to the patient population, type of SOT or SCT, and transplant center, with incidence ranging from 2 to 4.2 % and 5 to 10 %, following SCT or SOT, respectively [1–3]. The importance of CNS OI lies in their potential for profound morbidity and high mortality. Heightened clinical suspicion, early diagnosis, and prompt institution of therapy are paramount for successful outcome of these infections.

OIs in Transplantation: General Considerations

Neurologic events affect up to 40 % of transplant recipients, with serious complications occurring in up to 30 % [4–6]; hence, it is common for the neurologist to encounter a transplant recipient with altered sensorium, weakness, or seizure. The complexity of the transplant patient, with co-existing

metabolic and systemic infectious processes occurring simultaneously, may obscure the presence of CNS infection and make recognition of the process more challenging [5]. Immunosuppression may blunt traditional toxic signs and symptoms, and may alter cerebrospinal fluid (CSF) findings, resulting in subtle and atypical presentations.

The timing of infection with respect to the transplant is an important consideration. Following SOT, risk intervals for infections are categorized into three time periods [7]. During the early post-transplant period, in the first month following transplant, CNS infections are infrequent and more often due to herpes simplex virus (HSV) and *Aspergillus*, or infection transmitted by the organ donor [8–11]. Most OI occur between 2 and 6 months post-transplant, coinciding with the maximal effects of immunosuppression. Cytomegalovirus (CMV), *Cryptococcus*, and *Mycobacterium tuberculosis* (MTb) occur as a result of reactivation of latent infection in the recipient, donor transmission, or community acquisition. In the late post-transplant period, when immunosuppression is reduced, OI risk is lower, but may still occur. Risk is modified by anti-infective prophylaxis, intensity of immunosuppression, and allograft rejection.

Following SCT, infection risk varies with type of transplant, source of stem cells, chemotherapeutic conditioning, GVHD, GVHD prevention and treatment, and anti-infective prophylaxis. In the month following chemotherapy and before engraftment of stem cells, neutropenia is associated with bacterial, fungal, and HSV infections. In the second and third post-transplant months, OI with *Aspergillus,* John Cunningham virus (JCV), and CMV occur owing to impaired cellular immunity. Beyond 3 months, especially with chronic GVHD, infections with encapsulated bacteria, *Nocardia*, fungi, JCV, and herpesviruses occur [12].

Geographic and environmental exposures of both recipient and donor add important clues, especially for tuberculosis, the endemic mycoses, and toxoplasmosis. Concomitant lung disease, viral exanthema, and other skin lesions may also provide important diagnostic clues.

Major Nervous System Pathogens in the Transplant Recipient

Transplant patients have enhanced susceptibility to a broad range of CNS infections (Table 1).

Viral Infections

CNS viral infections are uncommon in transplant patients. Among 2,628 patients receiving allogeneic SCT only 32 (1.2 %) had documented viral encephalitis. More than one virus was identified in 16 %. Median time to onset was 106 days post-transplant (range 27–1,340 days). Infection with human herpesvirus-6 (HHV-6) occurred earliest (median 62 days; range 27–689 days) and progressive multifocal leukoencephalopathy (PML) had the longest median onset (334 days, range 107–1,340 days); 55 % had grade II or higher GVHD; and 34 % were taking prophylactic acyclovir or valacyclovir. Alteration of consciousness occurred in 81 %, seizures in 34 %, confusion, psychosis or personality changes in 28 %, and paresis in 25 %. CSF pleocytosis was seen in 48 % and elevated CSF protein in 46 %. Estimated encephalitis-related 1-year survival was 55 % [13•].

HHV-6

HHV-6 is a beta herpesvirus, commonly acquired early in life. HHV-6B is responsible for most infections. Two cases of HHV-6A encephalitis appear to be manifestations of a primary infection resulting from viral transmission through donor tissue [14, 15]. HHV-6 can be found in human brain at autopsy in individuals without a history of encephalitis, indicating long-term latency [16]. Plasma reactivation with HHV-6 DNA load>10,000 copies/ml has been associated with encephalitis [17]. Active HHV-6 encephalitis has been demonstrated in autopsied patients following SCT with HHV-6 DNA in CSF [18, 19].

Post-transplantation acute limbic encephalitis has been described with HHV-6B following allogeneic and cord blood SCT, typically appearing 3–4 weeks post-SCT, with acute onset of anterograde memory dysfunction, confusion, agitation disorientation or depressed sensorium, and seizures. Neurologic examination may be otherwise unremarkable.

Magnetic resonance imaging (MRI) demonstrates bilateral lesions in the anterior hippocampus, uncus, and amygdala. Electroencephalograms may reveal epileptiform or slow wave activity. CSF cell counts may be normal or reveal a mild lymphocytic pleocytosis and increased protein. HHV-6 DNA is variably recovered from CSF. The syndrome of inappropriate antidiuretic hormone secretion can occur [20–22]. Post-transplantation acute limbic encephalitis has been seen following SOT [23]. Neuropathologic studies demonstrate neuronal loss and gliosis in hippocampus, amygdala, mammillary bodies, and thalamus, with evidence of HHV-6 genome or immunoreactivity in astrocytes and neurons [18–20, 22]. HHV-6 myelitis has also been described [24].

Foscarnet, ganciclovir, and cidofovir all have inhibitory effects on HHV-6 *in vitro*, and have been employed in patients with HHV-6 encephalitis, sometimes in combination. Ganciclovir can be myelosuppressive, and foscarnet has renal toxicity, which may complicate therapy [25]. Outcomes of treatment have varied widely. One review cited a 43 % apparent full recovery rate [21]; however, another reported good cognitive recovery in only 2/8 patients [26]. Severe generalized epilepsy appearing 11–18 months

Table 1 Important central nervous system pathogens in transplant recipients

Pathogen	Syndromes	Predisposing conditions, risk factors and distinguishing features	Key diagnostic findings	Initial therapy of choice
Viruses				
Cytomegalovirus (CMV)	Encephalitis Myelitis	Prolonged T-cell depletion, recurrent CMV viremia ganciclovir-resistant strains >100 CMV DNA copies / 100,000 blood cells	Ependymitis on MRI CSF CMV DNA	Ganciclovir Foscarnet Combination Cidofovir + probenecid
Herpes simplex virus (HSV)	Focal encephalitis (HSV1), Meningoencephalitis (HSV2)		CSF HSV DNA	Acyclovir
		CSF VZV DNA		
Varicella zoster virus (VZV)	Meningitis Encephalitis Myelitis Vasculopathy with infarction	GVHD, corticosteroids, prolonged immune suppressive therapy, shorter duration prior antiviral therapy		Acyclovir Foscarnet Ganciclovir
Epstein–Barr virus (EBV)	Encephalitis Myelitis	>100 copies EBV DNA / 100,000 blood cells Systemic features distinguish PTLD	CSF EBV DNA	Ganciclovir Foscarnet
Human herpesvirus 6 (HHV-6)	Limbic encephalitis Myelitis	Plasma HHV-6 DNA>10,000 copies/ml Cord blood transplantation Glucocorticoids, SIADH	MRI abnormalities: uncus, amygdala, entorhinal area, hippocampus CSF HHV-6 DNA	Ganciclovir Foscarnet combination
Human herpesvirus 7 (HHV-7)	Encephalitis Myelitis		CSF HHV-7 DNA	Ganciclovir Foscarnet
John Cunningham virus (JCV)	Progressive multifocal encephalitis, occasional monofocal presentations	Prolonged T-cell depletion	CSF or tissue JCV DNA	Reduction of immune suppression
BK virus (BKV)	Encephalitis Meningitis	Hemorrhagic cystitis Interstitial nephritis	CSF or tissue BKV DNA with primers distinct from JCV	Reduction of immune suppression
Bacteria				
Nocardia spp.	Brain abscess Meningoencephalitis Myelitis Parkinsonism	Concomitant lung disease SOT: corticosteroids, lymphocyte depleting Abs SCT: corticosteroids; CMV infection	Brain biopsy with histopathology, Gram stain, and bacterial culture	TMP-SMX + imipenem or third-generation cephalosporin + amikacin
Listeria monocytogenes	Meningoencephalitis Brain abscess Rhomboencephalitis	SIADH SOT: corticosteroid, lymphocyte-depleting Abs, rejection SCT: corticosteroid, T-cell depleted grafts, HLA-mismatch grafts, GVHD	Blood culture, CSF Gram stain, and bacterial culture	Ampicillin or penicillin G + gentamicin
Mycobacterium tuberculosis (MTb)	Meningitis Brain abscess Tuberculoma	Disseminated disease, IRIS SOT: lymphocyte-depleting Abs, DM, CMV or *Nocardia*, latent MTb SCT: allogeneic SCT, GVHD, total body irradiation	CSF/tissue AFB smear/ culture; CSF MTb DNA	Isoniazid + rifabutin + pyridoxine + pyrazinamide + ethambutol
Fungi				
Aspergillus spp.	Brain abscess(es) Rhinocerebral infection Meningitis	Concomitant lung disease. SOT: *Aspergillus* airway colonization (lung), hypogammaglobulinemia (lung), re-transplantation (liver), re-operation (liver, heart), CMV (lung, heart), corticosteroids (kidney) treatment of rejection (all) SCT: neutropenia, GVHD, corticosteroids.	Brain biopsy with histopathology and fungal smear and culture	Voriconazole

Table 1 (continued)

Pathogen	Syndromes	Predisposing conditions, risk factors and distinguishing features	Key diagnostic findings	Initial therapy of choice
Mucorales	Rhinocerebral infection Brain abscess(es)	Mucosal black eschar SOT: re-transplant, DM, renal failure, iron overload SCT: GVHD, corticosteroids, CMV, respiratory virus, DM, malnutrition	Histopathology and fungal smear/ culture of infected tissue	Liposomal-AmB +/− echinocandin
Cryptococcus spp.	Meningitis Cryptococcoma(s)	Elevated ICP, IRIS, rare after SCT	CSF cryptococcal antigen, CSF fungal smear/ culture	Liposomal-AmB+/- flucytosine
Protozoa				
Toxoplasma gondii	Cerebritis/brain abscess Meningoencephalitis Spinal cord abscesses	Donor-derived infections occur; disseminated infections are common. SOT: heart recipients; D+/R– serostatus. SCT: R+ serostatus, unrelated donor, GVHD	Histopathology, PCR detection of *Toxoplasma* DNA in tissue	Sulfadiazine + pyrimethamine +leucovorin

GVHD graft versus host disease, *PTLD* post-transplantation lymphoproliferative disorder, *SIADH* syndrome of inappropriate antidiuretic hormone secretion, *SOT* solid organ transplantation, *SCT* stem cell transplantation, *Abs* antibodies, *HLA* human leukocyte antigen, *IRIS* immune reconstitution inflammatory syndrome, *DM* diabetes mellitus, *SCT* XXX, *ICP* intracranial pressure, *MRI* magnetic resonance imaging, *CSF* cerebrospinal fluid, *AFB* acid fast bacteria, *PCR* polymerase chain reaction, *TMP-SMX* trimethoprim-sulfamethoxazole, *LF-AmB* lipid formulations of amphotericin B, *D/R* donor/recipient

following SCT in three children accompanied by developmental regression and medial temporal atrophy on MRI has recently been described [27].

HHV-7

HHV-7 is a rare cause of neurologic disease. A case of brainstem encephalitis has been described in a child undergoing SCT. Despite treatment with ganciclovir, the child suffered rapid progression of bulbar dysfunction and a fatal cardiorespiratory arrest. Neuropathological examination demonstrated hemorrhages and neuronal degeneration in brain stem nuclei and periaqueductal gray matter, with HHV-7 DNA restricted to these regions [28].

Myelitis in a 47-year-old man, approximately 6 months after SCT, with fever, urinary retention, and spastic paraparesis, has been reported. Imaging of brain and spinal cord was unrevealing, but CSF revealed lymphocytic pleocytosis, elevated protein, and HHV-7 DNA. Following treatment with a 3-day pulse of intravenous methylprednisolone, the neurologic symptoms resolved [29].

CMV

CNS CMV infections are uncommon following SCT. Risk factors for encephalitis include prolonged T-cell depletion, recurrent CMV viremia, and ganciclovir-resistant strains [30]. Neurologic onset is usually acute with cognitive deterioration, visual disturbances, and progressive depression of sensorium. MRI may reveal a viral ependymitis. CSF may be normal or reveal pleocytosis and elevated protein, with recovery of CMV DNA. Despite therapy with combinations of ganciclovir, foscarnet, and cidofovir, mortality is high [30–32]. Resistance to ganciclovir has been demonstrated in recovered CMV isolates [30, 33]. A patient responding to treatment with foscarnet, cidofovir, and CMV hyperimmune globulin has been reported [34].

Varicella- Zoster Virus

Varicella-zoster virus (VZV) reactivation is common following both SCT and SOT. After allogeneic SCT, VZV infections occurred in 33 % following cessation of acyclovir or ganciclovir prophylaxis [35]. In 869 patients receiving SOT, VZV infection occurred in 8.6 % [36]. Despite the frequency of VZV infection following transplantation, CNS infection is relatively rare. A 2012 review identified only 12 cases in patients undergoing SCT, including a patient who developed meningitis and myelitis almost 2 years later, associated with cutaneous zoster eruption [37]. VZV meningitis and vasculopathy is associated with ischemic infarctions and inflammatory CSF containing VZV DNA [38, 39]. Although most VZV strains are sensitive to acyclovir, occasional patients may require foscarnet [40].

Epstein–Barr Virus

Epstein–Barr Virus (EBV) is an uncommon cause of CNS infection following transplantation. More than 100 copies of EBV DNA/100,000 cells in the blood have been associated

with risk of encephalitis [41]. EBV reactivation is more commonly associated with a multi-system post-transplantation lymphoproliferative disorder (PTLD), which may involve the CNS. Isolated cases of PTLD confined to the CNS are difficult to distinguish from EBV encephalitis in the absence of histology, as clinical, imaging, and CSF findings may overlap. The distinction is of importance as rituximab is recommended for treatment of PTLD or systemic EBV reactivation in patients following transplantation [42•, 43].

EBV encephalitis has been described as long as 8 years after SOT, presenting with alterations of sensorium with or without seizures. CSF pleocytosis is variable, but CSF may reveal EBV DNA. MRI may reveal lesions involving both gray and white matter. Discontinuation of immunosuppression coupled with antiviral therapy, employing ganciclovir, foscarnet, or cidofovir, has been associated with clinical and imaging resolution [44–47].

HSV

HSV encephalitis is uncommon after transplantation. Only four cases of HSV encephalitis were identified in a large series, occurring between 42 and 189 days post–transplant [13•]. Presentations include alterations of sensorium and fever, sometimes with headache, seizure, and signs attributable to CNS parenchyma or cranial nerves. CSF typically reveals lymphocytic pleocytosis, and diagnosis is established by recovery of HSV DNA from the CSF. MRI may or may not reveal frontal or temporal lesions. Treatment with acyclovir or similar agents is usually successful [13•, 48, 49].

JCV

PML results from lytic infection of oligodendroglia by JCV, a polyoma virus, resulting in demyelination, and CNS symptoms and signs reflecting the location of the lesions. The disease is believed to result from reactivation of latent JCV infection in immunosuppressed patients. JCV can be recovered from urine and blood from individuals without PML, and is believed to exist latently in the genital urinary tract and the bone marrow. Whether latent virus exists in the CNS is controversial.

A recent review identified 69 cases of PML including, 44 in individuals post-SOT and 25 post-SCT. No specific immune agent had an increased association. The interval between transplantation and onset of PML varied widely. Median time to onset was shorter in SCT (11 months) than SOT recipients (27 months); however, median survival was longer in SCT (19.5 months) than SOT (6.4 months). The case fatality rate was 84 %, with a 1-year survival of 56 % [50••]. An earlier review reported a median time to onset of 17 months with 71 % occurring within 24 months, and a mortality of 71 % within 2.5 months of PML onset [51]. A review of PML in 13 renal recipients reported a median onset of 37 months (range 5–120 months) [52].

Features of PML include progressive impairments of cognition, strength, balance, and central visual function. Seizures may be the first symptom prompting recognition. MRI typically reveals single or multiple, enhancing or non-enhancing, lesions in cerebral hemispheres, brainstem, and/or cerebellum. Deep gray matter structures may be involved. Diagnosis is established by demonstration of JCV DNA in CSF or tissue obtained by brain biopsy [50••, 51].

The only known treatment for PML is the reversal of immune suppression. Discontinuation of immune suppressive agents has been associated with stabilization of neurologic symptoms and survival [52, 53]. Other agents anecdotally administered to patients with PML include cytarabine, cytosine arabinoside, interleukin-2, mirtazapine, and mefloquine; however, none have demonstrated efficacy in controlled trials [50••].

BK Virus

BK virus (BKV) is a polyoma virus similar to JCV, which is known to establish latency in renal epithelial cells and may cause hemorrhagic cystitis and interstitial nephritis. Post-transplant reactivation occurs most commonly following renal transplantation. BKV has been variably recovered from astrocytes and ependymal cells, and CNS latency is uncertain [54]. CNS infections with BKV are rare, but have been reported following both kidney and stem cell transplants with nonspecific neurologic symptoms, including progressive confusion lethargy, or seizures. MRI may reveal lesions involving cerebral white matter, cerebellum, and deep gray structures [55–57]. Diagnosis depends on demonstration of specific BKV DNA with primers that exclude the closely related JCV [56]. Withdrawal of immune suppression may be accompanied by clinical response [55, 58].

Donor-Derived Viral Infections

A number of CNS infections in transplant recipients have been traced to transplanted tissues. Transmission of West Nile virus has been reported with SOT and SCT. Neurologic presentation may include fever and altered sensorium, tremors, and lower extremity paresis. CSF shows mixed polymorphonuclear and mononuclear pleocytosis. Diagnosis is established by the presence of West Nile virus-specific IgM antibodies. Treatment has generally been supportive with reduction of immune suppression; however, the course may be more severe and prolonged compared with the non-immune suppressed population [8, 59, 60]. A recent report describes apparent response to treatment with intravenous immune globulin [61].

Rabies has also been transmitted through transplanted organs, resulting in fatal encephalitis within 1 month of transplant [9, 62]. LCMV [10] and human T-cell lymphotropic virus type 1-associated myelopathy [63, 64] have also been transmitted through infected organs.

Bacterial Pathogens

Transplant patients are susceptible to CNS infections with pathogens found in hospitalized populations, such as *Streptococcus pneumoniae*, *Staphylococcus aureus*, and gram-negative bacilli [4, 6, 65, 66]. In addition, deficiencies of cellular immunity increase risk for nocardiosis, listeriosis, and tuberculosis [67–73].

Nocardia Species

Nocardiosis following SOT and SCT occurs in up to 3.5 % and 1.75 % of patients, respectively [70, 74]. High-dose corticosteroids are an important risk factor [67, 74, 75]; other risk factors include lymphocyte-depleting antibody therapies and CMV infection [70].

Nocardia is acquired via inhalation and disseminates hematogenously to the CNS, bone, and skin. Brain abscess is the most common CNS presentation, with symptoms including fever, headache, altered sensorium, and seizures. Uncommonly, Parkinsonism, meningoencephalitis, and spinal cord abscess occur [69].

Diagnosis requires culture of the bacteria from affected sites. In the absence of other systemic disease, brain biopsy with culture may be necessary to establish the diagnosis [68–70].

The treatment of CNS nocardiosis includes regimens with two or three antibiotics such as trimethoprim–sulfamethoxazole, imipenem, or a third-generation cephalosporin, and amikacin initially, until antimicrobial susceptibility testing results can guide therapy [68]. Susceptibility testing is crucial in antibiotic selection, as some species have high rates of sulfonamide resistance [70]. Reversal of immunosuppression is beneficial. Surgical intervention is reserved for refractory cases. Even with therapy, nocardiosis remains serious, with a high mortality rate [75].

Listeria Monocytogenes

Listeria monocytogenes is acquired by ingestion of contaminated foods and can result in systemic illness [71]. SOT is an important risk factor for acquisition [71]; however, association with SCT is less frequent unless T-cell depleted grafts, human leukocyte antigen-mismatched transplants, GVHD, or high-dose corticosteroid therapy are present [76, 77]. In SOT, corticosteroid or lymphocyte-depleting antibody therapies and allograft rejection are common predisposing factors [78]. With the exception of outbreaks [78], the post-transplant prevalence of listeriosis is low (up to 0.2 %) [77, 79, 80]; however, 70 % present with non-specific meningitis or meningoencephalitis, with fever; headache; altered sensorium; nuchal rigidity; and nausea, vomiting, and seizures [81]. Cranial neuropathies, dysarthria, paresis, and ataxia occur in approximately 40 % [71, 81]. CSF demonstrates variable polymorphonuclear or lymphocytic pleocytosis, elevated protein, and variable hypoglycorrhachia. *Listeria* encephalitis can mimic HSV. *Listeria* is seen on CSF Gram stain in only 30–40 % of cases [71, 81]. The syndrome of inappropriate antidiuretic hormone secretion is another frequent finding [81].

Listeria can also cause focal abscesses in the basal ganglia, thalamus, or medulla. In 25 % of such cases, there is concomitant meningitis. *Listeria*-associated rhomboencephalitis and spinal cord abscesses are rare [71].

The diagnosis of listeriosis is confirmed by culture in CSF and blood, with a yield of >80 % and 46–78 %, respectively [71, 81]. Empiric treatment, including parenteral ampicillin or penicillin, is recommended whenever *Listeria* is a diagnostic consideration, and for a minimum of 21 days when confirmed [82]. Initially, gentamicin is added for synergy [71]. Alternative agents are trimethoprim–sulfamethoxazole or meropenem [71, 82]. Surgical and intrathecal antibiotic therapies are reserved for refractory cases [71]. The mortality after transplantation ranges from 0 to 50 % [6, 78–80, 83].

M. tuberculosis

MTb infection is uncommon following SCT and SOT other than in endemic areas [73, 84–86]; however, the prevalence is 20–74 times higher in the transplant than in the general population [73, 87] Cases usually occur during the first year post-transplant and result from reactivation of latent infection, although donor-acquired or *de novo* infections also occur [73, 86, 88, 89].

Meningitis, or brain abscess, is rarely described post-SCT, but following SOT, up to 3 % will have meningitis and 1 % will have abscesses or tuberculomas. The CNS can be the sole site of infection [85, 90]. Fever occurs in virtually all cases [88, 89]. With meningitis, patients present with fever and altered mental status, but a minority have nuchal rigidity. Meningitis can be complicated by hydrocephalus and vasculopathy [89]. Tuberculous abscesses, >3 cm in diameter, seen in up to 28 % of SOT patients, present with fever, headache, seizures, and focal deficits. Tuberculomas can arise throughout the brain and spinal cord, and epidural, subdural, and subarachnoid spaces [87]. Fifty percent of patients with abscesses and tuberculomas will have meningitis concomitantly.

MRI may demonstrate basilar meningeal enhancement in patients with tuberculous meningitis. Abscesses and

tuberculomas may be accompanied by ring enhancement and surrounding edema. CSF usually reveals a lymphocytic pleocytosis with low glucose and elevated protein; however, variations occur, including normal CSF. Acid-fast stains are only positive in 10–40 % of cases, and yield may be increased with sampling larger volumes of CSF. Polymerase chain reaction detection of *M. tuberculosis* may be helpful, with a reported sensitivity of 4–100 % and specificity approaching 100 %. Diagnosis of tuberculosis is established by biopsy and culture of sites of infection. When pulmonary MTB is not present, brain biopsy may be necessary to establish the diagnosis [87].

Empiric treatment is warranted when CNS tuberculosis is suspected, and four-drug therapy is administered, including isoniazid, rifabutin, ethambutol, and pyrazinamide. Rifabutin replaces rifampin to minimize drug interactions [73, 87]. Some experts prefer a fluoroquinolone instead of rifabutin [88]. Nine to 12 months of therapy is recommended, and some extend the duration to 2 years for those with slow clinical response. Adjunctive dexamethasone is recommended for meningitis [87], as is reduction of immunosuppression, with serial CSF monitoring until normalization. Acute worsening of symptoms attributed to immune reconstitution inflammatory syndrome may occur 1–2 months following the initiation of therapy [87]. Mortality can exceed 40 % [87, 90].

Fungal Pathogens

Aspergillosis is the leading cause of brain abscesses in transplant recipients [1, 4, 66, 91]. *Cryptococcus* is the most important fungus causing meningoencephalitis following SOT [6]. *Candida* species are now infrequent intracranial pathogens [1, 4, 91, 92]. Emerging pathogens, such as *Pseudallescheria* species, *Scedosporium angiospermum*, and *Cladophialophora bantiana*, are occasional causes of brain abscess, especially in the highly immunosuppressed patient [65, 66, 91]. Occasional cases of meningitis or abscesses result from endemic mycoses, histoplasmosis, coccidioidomycosis, and blastomycosis [93].

Aspergillus Species

Invasive aspergillosis (IA) is acquired by inhalation, and the CNS is the most common target of hematogenous spread [94]. Hence, in the majority (75 %) of CNS cases, concomitant lung disease is evident, and up to 50 % of IA cases involve the CNS [95, 96]. CNS aspergillosis may also result from direct extension of invasive sinus infection. The reported prevalence of CNS aspergillosis following SCT and SOT is 0.8–3 % and 0.5–0.8 %, respectively [1, 6, 96, 97].

Risks for IA following SCT are neutropenia, GVHD, and high-dose corticosteroids [95, 96]. Post-SOT, risks of aspergillosis depend on the organ transplanted (see Table 1) [97, 98]. The median onset post-SCT ranges from 49 to 347 days [1, 96]. In a recent multicenter registry, aspergillosis occurred at a mean of 184 days, with 80 % presenting within the first 3 years of SOT [99].

CNS aspergillosis presents with fevers, alterations of mental status, seizures, stroke, and focal neurologic deficits, and can progress rapidly [95–97]. MRI usually demonstrates ring-enhancing or hemorrhagic lesions [96]. Diagnosis requires histopathologic, cytopathologic, or direct microscopic evidence of the fungus, with a culture positive for *Aspergillus* species. Serologic testing methods for measuring galactomannan antigen or 1,3-beta-d-glucan, support the diagnosis [94, 98]. An established diagnosis of invasive pulmonary or sinus aspergillosis combined with typical CNS imaging findings support presumptive diagnosis of cerebral aspergillosis. CSF examination usually reveals elevated protein; however, fungal smears and cultures are typically negative. Performing the galactomannan antigen or polymerase chain reaction DNA detection with CSF may have utility [100, 101].

First-line therapy for aspergillosis is voriconazole, with salvage options including lipid formulations of amphotericin B, posaconazole, and itraconazole [94, 98]. Combination antifungal therapy is commonly utilized, but data demonstrating superior efficacy are limited [94, 98]. Drug interactions between the azole antifungal agents and calcineurin inhibitors and some anti-epileptic medications occur owing to inhibition of cytochrome P450 enzymes. Reduction of immunosuppression is also advised. For aspergillomas, surgical therapy is associated with improved outcomes [95, 98, 101]. Mortality from post-transplant CNS aspergillosis approaches 100 % [96, 97], although modestly improved outcomes, with survival rates of up to 27 %, have been achieved with voriconazole [101].

Mucorales Species

Mucormycosis has gained importance in transplant recipients, and now accounts for 2 % and 8 % of invasive fungal infections in SOT and SCT, respectively [102•]. Re-transplantation, diabetes mellitus, renal failure, and iron overload increase the risk of mucormycosis after SOT, while tacrolimus appears protective. Liver recipients are at highest risk for the infection. After SCT, risk factors include older age, GVHD, receipt of high dose corticosteroids, antecedent CMV or respiratory viral infection, diabetes mellitus, and malnutrition [102•, 103].

Mucormycosis is acquired by inhalation of fungal spores and is vasoinvasive, resulting in rapid progression of tissue necrosis and thrombosis. CNS mucormycosis occurs primarily through direct extension from rhino-sino-orbital infection characterized by fever, headaches, unilateral facial pain, nasal/sinus congestion, impaired vision, peri-orbital swelling, proptosis, and ophthalmoplegia. A black mucosal or cutaneous eschar is suggestive [104]. Extension into the brain results

in lethargy, cranial nerve palsies, thrombosis of the carotid artery with stroke, and seizures. Alternatively, mucormycosis can occur as isolated CNS disease or arise from dissemination from another site (e.g., lung) [105].

MRI may show cavernous sinus invasion or thrombosis, internal carotid artery thrombosis, or intracerebral abscesses. The diagnosis is established by histopathology and culture of necrotic tissue. Suspected mucormycosis requires emergent intervention with surgical debridements, antifungal therapy, reversal of immunosuppression, and correction of hyperglycemia. Liposomal amphotericin B is the treatment of choice, sometimes in combination with an echinocandin. Posaconazole is a salvage option [102•]. Mortality approaches 100 %, although limited data suggest better outcomes with combination therapy [105, 106].

Cryptococcus Species

Cryptococci are ubiquitous yeasts, acquired by inhalation, which result in respiratory infection, and have a predilection for dissemination to the CNS. Cryptococcosis is exceedingly rare following SCT [107]; however, cryptococcal meningitis is a late complication of SOT, with a mean onset of 28 months post-transplantation [108]. Cases occurring in the first month post-SOT are thought to represent either reactivation of latent host disease or donor transmission [109]. Some patients may present with intracerebral cryptococcomas.

Subacute or chronic meningitis occurs in up to 60 % of SOT recipients with cryptococcosis. Symptoms include fevers, night sweats, weight loss, headaches, cranial neuropathies, impaired sensorium, nausea, and vomiting [108, 110]. Meningismus is infrequent; however, elevated intracranial pressure often complicates cryptococcal meningitis [108].

Diagnostic evaluation includes brain imaging for mass lesions, cerebral edema or hydrocephalus, and lumbar puncture, which may demonstrate elevated opening pressure, with variable CSF mononuclear pleocytosis, elevated protein, and low glucose [108, 111]. Diagnosis is based on rapid antigen detection in CSF and serum and isolation of the pathogen in CSF culture.

Induction therapy consists of lipid formulations of amphotericin B plus flucytosine for at least 2 weeks, followed by consolidation and maintenance therapy with fluconazole [112••]. Elevated intracranial pressure is managed with serial lumbar punctures and drainage of CSF, sometimes requiring lumbar drains or ventriculoperitoneal shunts [112••]. Reduction of immunosuppression is desirable to control infection, with corticosteroids reduced in preference to calcineurin inhibitors, which have known anti-cryptococcal activity [108, 112••]. Reductions must be performed judiciously to avoid immune reconstitution inflammatory syndrome [112••, 113]. Post-SOT mortality ranges from 30 % to 50 % [107, 108].

Longer durations of induction, consolidation, and maintenance therapy are required for cryptococcomas. Corticosteroids are recommended for surrounding edema. Surgical intervention is recommended for cryptococcomas >3 cm, and those causing mass effect [112••].

Protozoal Pathogens

CNS parasitic infections in transplant recipients occur in restricted geographic distributions, and *Toxoplasma gondii* is the most important pathogen [114, 115]. Meningoencephalitis, caused by *Acanthamoeba* and *Naegleria*, is occasionally reported [115].

Toxoplasma Gondii

Toxoplasmosis is less prevalent in the USA and Asia than in Europe, Africa, and Central and South America. Toxoplasmosis occurs by reactivation of latent disease, as a primary infection following ingestion of contaminated foods, or through transmission from blood or donor tissue, most notably heart, which may contain encysted parasites [115].

Toxoplasmic meningoencephalitis typically occurs in the first 3 months after transplant and can be rapidly fatal [115, 116, 117•]. In a recent SOT study, recipient seronegative status was the only risk factor identified [117•]. Following SCT, risks include seropositive recipients, unrelated donor SCT, and GVHD [116].

CNS toxoplasmosis may present with fevers, headache, seizures, decreased sensorium, and focal deficits [116]. *Toxoplasma* has a propensity for infecting basal ganglia and cerebrum, and MRI may demonstrate ring-enhancing lesions, edema, or hemorrhage. In heavily immunosuppressed SCT patients, lesions may fail to enhance [115]. Infrequently, meningoencephalitis or myelitis may occur [118].

Empiric therapy with sulfadiazine, pyrimethamine, and leucovorin is recommended on suspicion of the diagnosis. Presumptive diagnosis is based on seropositivity, clinical presentation, characteristic imaging, and response to anti-*Toxoplasma* therapy. CSF may show elevated *Toxoplasma*-specific IgG index or evidence of *Toxoplasma* DNA, but no diagnostic finding is specific other than histopathology [115, 119]. Following initial treatment, chronic suppressive therapy is required [115].

Conclusions

CNS OI in patients following SOT and SCT are rare, but serious, complications that increase post-transplant morbidity and mortality. Diagnosis is difficult in the complex milieu of the transplant setting, and prognosis—even with therapy—is guarded. This review has discussed pathogens seen in the

post-transplantation setting and suggested potential clues to facilitate diagnosis.

Compliance with Ethics Guidelines

Conflict of Interest Bruce A. Cohen and Valentina Stosor declare that they have no conflict of interest.

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

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- •• Of major importance

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