Central Nervous System Infections

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ABSTRACT This chapter provides an overview of infectious syndromes, pathogens, and diagnostic testing modalities for central nervous system infections in the immunocompromised host.

INTRODUCTION Infections of the central nervous system (CNS) are associated with significant morbidity and mortality, with outcome often dependent on the rapidity with which a pathogen is identified and appropriate therapy is begun. Immunocompromised hosts are at risk for CNS infections with both common microorganisms, which may present atypically in this population, and with opportunistic pathogens. The microbiologic causes of infection vary by syndrome (e.g., meningitis versus encephalitis) and specific impairment in immunity (e.g., deficits in T-cell function versus hypogammaglobulinemia). This chapter provides a framework for the assessment and laboratory evaluation of immunocompromised patients presenting with CNS infections. Detailed discussions of the individual agents are provided in the corresponding pathogen-specific chapters.

The CNS has several unique anatomic and immunologic characteristics that distinguish infection at this site. The brain and spinal cord are contained within the bony confines of the calvarium and vertebral column. Because of the spatial limitations imposed by these structures, inflammation and edema rapidly progress to ischemia and, in severe cases, cerebral herniation (1). The blood–brain barrier (BBB) comprises a tight endothelial lining which limits the penetration of many blood-borne pathogens into the CNS. However, the BBB also serves to limit the entry of leukocytes, complement, and immunoglobulin into the CNS, and the absence of these mediators of innate immunity contributes to the rapid progression and serious consequences of many CNS infections (2). In addition, antibiotics used to treat CNS infections must have pharmacologic properties allowing penetration of the BBB, and higher doses are often required to achieve bactericidal levels.

While this chapter is limited to CNS infections, it is important to recognize that noninfectious conditions may present in a similar fashion. For instance, posterior reversible leukoencephalopathy (PRES) is a noninfectious condition that presents with headache, seizures, altered mental status, and cortical blindness. PRES has been reported as a complication of both chemotherapy (3) and cyclosporine (4). Both trimethoprim-sulfamethoxazole (5), used for prophylaxis of Pneumocystis jirovecii pneumonia, and OKT3 (6), a monoclonal antibody used to reverse organ rejection, have been associated with aseptic meningitis. Immunocompromised patients are also at increased risk for CNS malignancies, including post-transplant lymphoproliferative disease and primary CNS
lymphoma. Failure to identify an infectious etiology should prompt consideration of one of these noninfectious processes.

**CLINICAL MANIFESTATIONS**

**Central Nervous System Infections**

The central nervous system is susceptible to infection from a wide array of microorganisms, including bacteria, fungi, viruses, protozoa, and prions. CNS infections are classified as involving the meninges (meningitis), brain parenchyma (encephalitis or mass lesion of the brain), or spinal cord (myelitis) based on the predominant anatomic site of infection, although significant overlap may exist (e.g., meningoencephalitis or encephalomyelitis). While these syndromes often present similarly, specific pathogens may be trophic for differing anatomic sites.

**Meningitis**

Meningitis is defined as inflammation of the protective membranes of the brain and spinal cord, known collectively as the meninges. The classic symptoms of meningitis are fever, headache, neck stiffness, photophobia, and occasionally mental status changes (7), but this syndrome may present atypically in the immunocompromised host (8, 9). Meningitis can be further subdivided by the time course of symptom onset, with the differential diagnosis guided by acuity of illness.

Acute meningitis is typically caused by bacterial or viral pathogens (Table 1). The same pathogens seen in immunocompetent patients, such as *S. pneumoniae* and enteroviruses, also predominate in the immunocompromised population. Acute bacterial meningitis is typically marked by high fevers and rapid decline in neurologic status in the absence of prompt antibiotic administration (10). Acute viral meningitis, on the other hand, is generally more insidious in onset, with symptom onset occurring over days rather than hours. Extraneurologic manifestations may be present in viral meningitis, such as genital lesions in herpes simplex virus 2 (HSV-2) meningitis and gastrointestinal disturbances with enteroviral meningitis, due to the tropism for both neuronal and extraneuronal tissues (11).

Conversely, subacute or chronic meningitis, which is characterized by symptom onset over a period of weeks to months, is seen predominantly in the immunocompromised host (12). Patients generally present with constitutional symptoms, such as generalized malaise, low-grade fevers, and weight loss. The classic meningeal symptoms of photophobia, neck stiffness, and mental status changes are often subtle in nature or occasionally absent. Chronic meningitis may be caused by fungal (*Cryptococcus, Histoplasma, Blastomyces, Coccidioides, Aspergillus*), mycobacterial (*Mycobacterium tuberculosis*), or atypical bacterial pathogens (*Treponema pallidum, Borrelia burgdorferi*) (12).

**Encephalitis and brain mass lesions**

Encephalitis is defined as inflammation of the brain parenchyma associated with neurologic dysfunction that classically includes aberrations in mental status (13). Other supporting signs and symptoms include fever, focal neurologic deficits (both motor and sensory), and seizures. Common associated findings include CSF pleocytosis, most commonly lymphocytic, and focal brain abnormalities on neuroimaging studies. Although viruses are the most common etiologic agents of encephalitis, in approximately half of all cases, no etiology is identified (14, 15). The array of causative organisms for encephalitis is broader in the immunocompromised patient population (Table 2). The clinical presentation can

<table>
<thead>
<tr>
<th>Class</th>
<th>Agent</th>
<th>Immune deficit or at-risk population</th>
<th>Preferred diagnostic test(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Viruses</strong></td>
<td>Enterovirus</td>
<td>Hypogammaglobulinemia, HIV (acute infection)</td>
<td>CSF PCR, RNA viral load whole blood</td>
</tr>
<tr>
<td></td>
<td>HIV</td>
<td>HIV infection</td>
<td>CSF culture, CSF antigen testing</td>
</tr>
<tr>
<td><strong>Bacteria</strong></td>
<td><em>S. pneumoniae</em></td>
<td>Hypogammaglobulinemia, asplenia, HIV infection</td>
<td>CSF culture</td>
</tr>
<tr>
<td></td>
<td><em>L. monocytogenes</em></td>
<td>T-cell impairment, steroid use</td>
<td>CSF culture, CSF VDRL, <em>M. tuberculosis</em> CSF PCR, CSF mycobacterial culture, culture of extraneural material</td>
</tr>
<tr>
<td></td>
<td><em>T. pallidum</em></td>
<td>HIV</td>
<td>Cryptococcal antigen (CSF), CSF fungal culture</td>
</tr>
<tr>
<td></td>
<td><em>M. tuberculosis</em></td>
<td>HIV infection, steroid use</td>
<td>CSF histoplasma antigen, CSF fungal culture, urine histoplasma antigen</td>
</tr>
<tr>
<td><strong>Fungi</strong></td>
<td><em>Cryptococcus neoformans</em></td>
<td>AIDS, steroid use</td>
<td>CSF Blastomyces antigen, CSF fungal culture, urine Blastomyces antigen</td>
</tr>
<tr>
<td></td>
<td><em>H. capsulatum</em></td>
<td>AIDS, steroid use</td>
<td>CSF Blastomyces antigen, CSF fungal culture, urine Blastomyces antigen</td>
</tr>
<tr>
<td></td>
<td><em>B. dermatitidis</em></td>
<td>AIDS, steroid use</td>
<td>CSF Coccidioides antigen, CSF fungal culture, serology</td>
</tr>
<tr>
<td></td>
<td><em>C. immitis</em></td>
<td>AIDS, steroid use</td>
<td></td>
</tr>
</tbody>
</table>
TABLE 2 Major infectious causes of encephalitis or mass lesions of the brain among immunocompromised hosts

<table>
<thead>
<tr>
<th>Class</th>
<th>Agent</th>
<th>Immune deficit or at-risk population</th>
<th>Preferred diagnostic test(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viruses</td>
<td>EBV&lt;sup&gt;a&lt;/sup&gt;</td>
<td>AIDS</td>
<td>Tissue biopsy, CSF cytology</td>
</tr>
<tr>
<td></td>
<td>HHV-6</td>
<td>Stem cell transplant</td>
<td>HHV-6 PCR CSF</td>
</tr>
<tr>
<td></td>
<td>CMV</td>
<td>AIDS</td>
<td>CMV PCR CSF</td>
</tr>
<tr>
<td></td>
<td>Rabies virus&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Solid organ transplant</td>
<td>Rabies antibody CSF, rabies PCR saliva, DFA nape of neck biopsy</td>
</tr>
<tr>
<td></td>
<td>Lymphocytic</td>
<td>Solid organ transplant</td>
<td>Serology</td>
</tr>
<tr>
<td></td>
<td>choriomeningitis virus&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>WNV&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Solid organ or stem cell transplant</td>
<td>CSF IgM antibody, CSF WNV PCR</td>
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<tr>
<td></td>
<td>JC virus</td>
<td>AIDS, monoclonal antibodies (e.g., Rituxan)</td>
<td>JC virus PCR CSF</td>
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<tr>
<td>Bacteria</td>
<td>L. monocytogenes</td>
<td>Steroid use</td>
<td>CSF culture</td>
</tr>
<tr>
<td></td>
<td>T. pallidum</td>
<td>HIV</td>
<td>CSF VDRL</td>
</tr>
<tr>
<td></td>
<td>M. tuberculosis</td>
<td>HIV</td>
<td>CSF PCR, mycobacterial culture; histopathology for tuberculosis</td>
</tr>
<tr>
<td></td>
<td>Nocardia</td>
<td>Steroid use, solid organ transplant</td>
<td>CSF culture, extra-neural cultures</td>
</tr>
<tr>
<td>Fungi</td>
<td>Cryptococcus neoformans</td>
<td>AIDS, steroid use</td>
<td>Cryptococcal antigen (CSF), CSF fungal culture</td>
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<td></td>
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<td>CSF Blastomyces antigen, CSF fungal culture, urine Blastomyces antigen</td>
</tr>
<tr>
<td></td>
<td>C. immitis</td>
<td>AIDS, steroid use</td>
<td>CSF Coccidioides antigen, CSF fungal culture, serology</td>
</tr>
<tr>
<td></td>
<td>Aspergillus spp.</td>
<td>Neutropenia, Stem cell transplant, solid organ transplant, steroid use</td>
<td>Culture, serum or CSF galactomannan assay; histopathology</td>
</tr>
<tr>
<td></td>
<td>Zygomycoses</td>
<td>Neutropenia, Stem cell transplant, solid organ transplant, steroid use use poorly controlled diabetes mellitus</td>
<td>Culture; histopathology</td>
</tr>
<tr>
<td>Protozoa</td>
<td>Toxoplasmosis&lt;sup&gt;b&lt;/sup&gt;</td>
<td>AIDS, solid organ transplant</td>
<td>CSF PCR, histopathology, toxoplasma antibodies (serum)</td>
</tr>
<tr>
<td></td>
<td>Acanthamoeba, Naegleria fowleri</td>
<td></td>
<td>Cytology, histopathology, CSF wet mount</td>
</tr>
</tbody>
</table>

<sup>a</sup>Primary CNS lymphoma.

<sup>b</sup>Cases associated with transplant of solid organ from infected donor.

be acute, as is the case with HSV-1 or arboviral encephalitis, or chronic, due to either a smoldering infection or reactivation of latent virus (e.g., John Cunningham [JC] virus, human herpes viruses). Demographic or epidemiologic findings may aid in guiding appropriate diagnostic testing. For instance, testing for Powassan virus, an emerging tick-borne virus endemic to the northern United States, in a patient without a compatible travel history would be anticipated to be low yield (16). In addition, clinical findings may be suggestive of a specific etiologic agent. For instance, vesicular skin lesions consistent with zoster might raise consideration of varicella zoster virus (VZV) encephalitis, while acute flaccid paralysis is a common manifestation of West Nile virus (WNV) encephalitis (11, 17, 18).

Mass or space-occupying lesions usually present with focal neurologic deficits that correspond to the site of infection (19). As development of a mass is typically an indolent process, symptom onset usually occurs over weeks to months for most patients. Once again, the differential diagnosis of infectious mass lesions in the immunocompromised host is significantly broader than in the immunocompetent host and includes bacterial (polymicrobial abscesses, Nocardia, M. tuberculosis), fungal (Cryptococcus, Aspergillus, Zygomycetes), protozoan (Toxoplasma gondii, Acanthamoeba, Microsporidia), and viral pathogens (Epstein-Barr virus [EBV]-associated primary CNS lymphoma). Diagnosis may be suggested by non-invasive testing, but often neurosurgical intervention is needed both for diagnostic and therapeutic purposes.

**Myelitis**

Myelitis is characterized by inflammation of the spinal cord that can be diffuse or localized to a specific region (Table 3). It typically presents as a variable combination of sensory loss, motor weakness, and autonomic instability that is manifested by bladder, bowel, and sexual dysfunction (20). Myelitis may occur in isolation or as an overlap syndrome with encephalitis or meningitis (21).

Acute myelitis, in which symptom onset occurs within hours to days, is most commonly caused by viral pathogens due to either an acute infection (primary HIV infection, WNV) or reactivation of a latent viral infection (herpes viruses). The clinical presentation may be suggestive of a specific etiologic agent. For instance, acute onset of lumbosacral polyradiculopathy in a patient with AIDS might suggest cytomegalovirus (CMV) myelitis, whereas subacute onset of lower extremity paraparesis...
in a transplant patient should raise suspicion for human T-lymphotropic virus (HTLV)-1 associated myelopathy (HAM). Chronic myelitis, on the other hand, is typically diagnosed in advanced AIDS and is due to microvacuolization of the spinal cord white matter rather than to a secondary opportunistic infection.

**IMMUNOCOMPROMISED STATUS AND SYNDROMES**

**HIV/AIDS**

The human immunodeficiency virus (HIV) infects CD4+ T lymphocytes and causes their destruction via lysis of infected cells or by inducing apoptosis, resulting in impaired cell-mediated immunity. HIV also causes dysfunction of B cells, monocytes, and natural killer cells, leading to diminished humoral and innate immune responses. These impairments in immune function increase the risk of infections with bacterial, viral, mycobacterial, fungal, and parasitic pathogens. The risk of opportunistic infection among HIV-infected patients varies according to the level of immune impairment. The incidence and microbiology of CNS infections in individuals with CD4 T-cell counts >200 cells/mm³ is similar to those seen in age-matched immunocompetent hosts, with bacterial and viral pathogens predominating. Sexually transmitted infections, such as syphilis and HSV, are relatively common due to behavioral risk factors. Individuals with CD4 counts <200 cells/mm³ are at increased risk for CNS infections due to endemic fungi (Histoplasma, Blastomyces, and Coccidioides spp.), JC virus (progressive multifocal leukoencephalopathy [PML]), toxoplasmosis, and tuberculosis. Risk of primary CNS lymphoma (often EBV related) is elevated in those with CD4 counts <100 cells/mm³. Cytomegalovirus encephalitis and cryptococcal meningitis are typically seen in HIV patients with CD4 counts less than 50 cells/mm³, and infection with multiple pathogens is not uncommon in this population (22). Medications, including highly active antiretroviral therapy (HAART) and antimicrobial prophylaxis, can reduce the risk of opportunistic infections. Trimethoprim-sulfamethoxazole, recommended as prophylaxis when the CD4 cell count declines below 200 cells/mm³, is protective against CNS infections due to *Toxoplasma, Nocardia,* and *Listeria.*

HIV itself is a neurotropic virus that crosses the blood–brain barrier via monocytes and subsequently infects microglial and neuroepithelial cells of the CNS (23). Aseptic meningitis can be the sentinel presentation of acute HIV infection (24). Immune reconstitution syndrome should be considered in patients who develop neurologic symptoms within 12 weeks of initiation of HAART, particularly in the setting of a known CNS infection. Chronic infection and inflammation from HIV can lead to a spectrum of cognitive and motor dysfunction, called HIV-associated neurocognitive disorder, which can occur despite treatment with HAART (23, 25, 26).

**Transplant**

The risk of CNS infection following solid organ transplantation varies depending on type of organ transplanted, specific induction and maintenance immunosuppression, and time of onset posttransplant. There are three general mechanisms of these infections: (i) transmission from an infected donor organ; (ii) reactivation of latent infection; or (iii) acute infection following transplantation. In general, the first year following transplantation carries the highest risk for opportunistic infections as the effects of induction immunosuppression typically last for 3 to 6 months. Target levels for maintenance immunosuppression are typically higher for the first year posttransplant as this is the most common time for rejection to occur. Pretransplant serologic screening of both the recipient and donor can help to stratify the risk of particular infections and to guide decisions regarding prophylaxis.

Standard prophylaxis regimens are typically given to mitigate the risk of some of the most common post-

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**TABLE 3** Infectious causes of myelitis among immunocompromised patients

<table>
<thead>
<tr>
<th>Class</th>
<th>Agent</th>
<th>Immune deficit or affected population</th>
<th>Diagnostic test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viruses</td>
<td>WNV*</td>
<td>Solid organ transplant</td>
<td>CSF serology (IgM)</td>
</tr>
<tr>
<td>HIV (acute or chronic)</td>
<td>CMV</td>
<td>AIDS, solid organ transplant, stem cell transplant</td>
<td>CMV PCR CSF</td>
</tr>
<tr>
<td>EBV</td>
<td>EBV</td>
<td>Solid organ transplant, stem cell transplant</td>
<td>Histopathology</td>
</tr>
<tr>
<td>VZV</td>
<td>VZV</td>
<td>AIDS, solid organ transplant, stem cell transplant, steroid use</td>
<td>EBV PCR CSF</td>
</tr>
<tr>
<td>HTLV-1*</td>
<td>HTLV-1</td>
<td>Solid organ transplant</td>
<td>VZV PCR CSF, VZV antibodies CSF</td>
</tr>
<tr>
<td>Bacteria</td>
<td><em>T. pallidum</em></td>
<td>HIV</td>
<td>HTLV PCR CSF</td>
</tr>
<tr>
<td></td>
<td><em>M. tuberculosis</em></td>
<td>HIV</td>
<td>Mycobacterial PCR CSF, mycobacterial culture</td>
</tr>
</tbody>
</table>

*Cases associated with transplant of solid organ from infected donor as well as acquired infection in previously immunocompromised host.
In summary, there are three distinct periods following hematopoietic stem cell transplantation during which the recipient is at increased risk for specific pathogens. The first is the preengraftment period, which begins with the conditioning regimen and continues until engraftment occurs, usually between 10 and 40 days. During this period of leukopenia, recipients are susceptible to bacterial and fungal pathogens (including early invasive molds), as well as to reactivation of herpes viruses. The incidence of CNS infection during this period is relatively low as patients are often receiving antimicrobial prophylaxis. Following the preengraftment period is the postengraftment period, which persists for the first 100 days following engraftment. While the patients are no longer leukopenic during this time, they still have abnormal humoral and cell-mediated immunity and are susceptible to CNS infections caused by the herpes viruses, Toxoplasma, filamentous and dimorphic fungi, and bacteria (particularly Listeria, Nocardia, and encapsulated organisms). Recipients of an allogeneic graft also generally receive prophylaxis against GVHD, which leads to further immunosuppression. The late risk period follows the postengraftment period and extends until the patient has regained near-normal immune function and no longer requires therapy for GVHD. There may still be deficiencies in cell-mediated and/or humoral immunity during this period. GVHD and its treatment are associated with a high risk of infections due to herpes viruses (particularly HSV, VZV, and CMV) as well as invasive fungal infections without antimicrobial prophylaxis.

**Other Immunocompromising Conditions**

Biologic agents are increasingly used to treat a variety of autoimmune and systemic inflammatory processes and can predispose patients to opportunistic infections. The tumor necrosis factor alpha inhibitors interfere with activation of macrophages, phagosomes, recruitment of neutrophils, and formation and maintenance of granulomas. The agents predispose patients to CNS infections with Listeria and Nocardia spp., endemic fungi, tuberculosis, and herpes viruses. Rituximab is a monoclonal antibody that targets the CD20 antigen on lymphocytes, resulting in B cell depletion. Treatment with this agent is associated with reactivation of viral infections, particularly the JC virus. Patients with splenectomy, complement deficiencies, or those receiving complement inhibitors are at increased risk of infection due to encapsulated bacteria, including Neisseria meningitidis, Streptococcus pneumoniae, and Haemophilus influenzae.

Glucocorticoids alter innate and acquired immunity by suppressing function of neutrophils and lymphocytes and by inhibiting cytokine release. The level of immune impairment is based on steroid dose, length of treatment, the underlying medical problem, and concurrent use of immunosuppressive agents, including calcineurin inhibitors. The diagnosis of PRES is suggested by the presence of symmetric white-matter edema localized to the parieto-occipital region, cerebellum, or brainstem. These abnormalities are best appreciated on MRI scan with diffusion-weighted images, and as the name suggests, they resolve over weeks to months following discontinuation of the implicated medication.

In hematopoietic stem cell transplantation, there are a multitude of factors that influence individual risk of infection, including recipient age, the underlying disease, source of the stem cells (i.e., autologous, allogeneic, or cord blood), type of conditioning regimen, timing of engraftment, and need for graft-versus-host disease (GVHD) prophylaxis or treatment. Myeloblastic conditioning, delayed or failed engraftment, mismatched or unrelated donor, and acute myeloid leukemia as well as myelodysplastic syndromes are associated with a longer duration of neutropenia, which impacts patients’ risk of bacterial and fungal infections. Recipients of autologous stem cell transplants have a shorter period of neutropenia compared to allogeneic and cord blood recipients. Humoral immune function remains relatively intact in these patients and there is much faster recovery of cell-mediated immunity. Conversely, cord blood recipients have the longest duration of neutropenia, and due to the naïve nature of their graft, they do not acquire humoral immunity from their donor, placing them at risk for various bacterial and viral pathogens, particularly human herpes viruses. Some patients have hypogammaglobulinemia following HSCT and require supplemental IgG and antibiotic prophylaxis to prevent bacterial infections.
of additional immunosuppressants. Diabetes mellitus, renal failure, pregnancy, chronic alcohol use, liver failure, and malignancy all impair specific functions of the immune systems and have been associated with increased risk for CNS infections.

**CNS PATHOGENS**

**Bacteria**

**Hospital-acquired infections**

Immunocompromised patients, through the nature of their underlying illnesses, have significant interactions with the healthcare system, translating into an increased risk for infection with hospital-acquired, often multidrug-resistant bacteria (38, 39). This may occur through bacteremia with secondary seeding of the CNS or through direct infection associated with instrumentation. For example, patients with leptomeningeal malignancies often require a reservoir for intraventricular administration of chemotherapy and are therefore at risk for meningitis with both normal skin microbiota and hospital-acquired bacteria through inoculation into the cerebrospinal fluid (40, 41). Organisms associated with hospital-acquired central nervous system infections include methicillin-resistant S. aureus, vancomycin-resistant Enterococcus, enteric bacteria, Pseudomonas aeruginosa, and multidrug-resistant Acinetobacter (42).

**Encapsulated organisms**

*S. pneumoniae* and *N. meningitidis* are the most common causes of acute bacterial meningitis in both the immunocompetent and immunocompromised host. Individuals with impaired humoral immunity (including those with HIV infection) or asplenia are at particular risk for CNS infection with these agents (43). Widespread implementation of vaccination has led to a marked decrease in the incidence of meningitis due to these bacteria and underscores recommendations for routine pneumococcal immunization of patients with impaired immunity (44) and meningococcal immunization for patients with asplenia or complement deficiency (45). Historically, *H. influenzae* was a leading cause of pediatric meningitis. The incidence of this infection has decreased significantly following the introduction of *H. influenzae* type b (Hib) immunization, and most cases of *H. influenzae* meningitis are now due to nontypable strains (46, 47). Hib vaccination is recommended in previously unimmunized patients with asplenia, HIV-infected children (but not adults), and recipients of hematopoietic stem cell transplantation (48).

**Enteric and foodborne infections**

Foodborne bacterial infections are significant causes of central nervous system infections in immunocompromised patients. *Listeria monocyto genes* is a foodborne pathogen associated with ingestion of contaminated deli meats and dairy products, particularly Mexican-style cheeses (49). *Listeria* has particular tropism for the CNS, and it is an important cause of disease in the elderly and individuals with impaired T-cell immunity. While listeria infection of the CNS most commonly presents as meningitis, this bacterium may also cause rhomboencephalitis. National surveillance for invasive listeriosis identified an underlying medical condition in 74% of nonpregnant patients, with immunosuppressive therapy accounting for one-third of these cases (50). Trimethoprim–sulfamethoxazole, commonly prescribed in patients with cell-mediated immunodeficiency as prophylaxis for *Pneumocystis jirovecii*, is protective against listeria infection.

*Salmonella* meningitis is extremely uncommon in the immunocompetent host but has been reported in HIV-infected and transplant patients (51). Gram-negative bacterial meningitis is a rare complication of the *Strongyloides* hyperinfection syndrome, seen almost exclusively in patients on high-dose corticosteroids or other immunosuppressing medications (52, 53).

**Syphilis**

Infection with *Treponema pallidum* occurs with increased frequency in HIV, and in particular in men who have sex with men. Neurologic manifestations of early syphilis are common with HIV, and include meningitis, cranial nerve abnormalities, ocular disease, neurovascular disease, and cerebral gummata (54). HIV patients with early syphilis frequently have occult involvement of the CNS in the absence of neurologic symptoms, and therefore coinfected patients should either have routine lumbar puncture or be monitored closely for treatment failure, which would then necessitate CSF sampling (55). Late neurosyphilis develops years to decades after the initial infection and is characterized by dementia or ataxia due to involvement of the posterior column of the spinal cord, termed tabes dorsalis.

**Vector-borne and zoonotic bacteria**

Fulminant infection with *Ehrlichia chaffeensis*, a tick-borne infection endemic to the southeast and south-central United States, has been reported in HIV-infected individuals (56). Altered mentation is noted in approximately 30% of patients with human monocytic
ehrlichiosis, and the bacterium can be variably amplified from CSF. A closely related organism, E. ewingii, causes a milder febrile illness that occurs almost exclusively in immunosuppressed patients (57). Capnocytophaga canimorsus is a Gram-negative rod that is a normal component of canine oral microbiota and is associated with sepsis and meningitis after dog bites. This infection is particularly fulminant in asplenic hosts, with a mortality exceeding 25% (58).

Nocardia
Nocardia is a partially acid-fast Gram-positive rod that is widespread in the environment. More than 100 species have been identified, although human disease has been reported with a minority (59). Infection occurs through inhalation of the organism, with secondary hematogenous spread to the central nervous system. CNS disease is particularly common in patients who have had solid organ transplant and those on steroids, although in a large series, 18% of patients with CNS nocardia were immunocompetent (60).

While the most common cause of CNS disease is N. asteroides, which accounts for 35% of cases (60), N. farcinica is particularly neurotropic (61). This has important therapeutic implications as N. farcinica is resistant to a number of antibiotics commonly used to treat nocardiosis, including trimethoprim–sulfamethoxazole in up to 80% of cases (62). Radiographically, CNS nocardiosis presents as single or multiple ring-enhancing mass lesions of the brain (63). Patients with CNS nocardia infection often have concomitant pulmonary or cutaneous involvement, and biopsy of these more easily accessible sites may be diagnostic.

VIRAL PATHOGENS
CNS viral infections can present as meningitis, encephalitis, or myelitis, with significant overlap observed among these clinical syndromes. Viral pathogens may cause disease through acute infection (including donor-derived infection) or reactivation of latent infection. The risk of infection is dependent upon the degree of immunodeficiency and current or past exposure to the specific pathogen. The paragraphs below describe in greater detail specific viral pathogens responsible for CNS infection in immunocompromised hosts.

Herpes Viruses
Herpes viruses are the most ubiquitous cause of viral CNS infection in immunocompromised hosts and are capable of causing acute infection, establishing latency, and subsequentlyreactivating in the setting of immunodeficiency. Hosts with deficits in cell-mediated immunity (HIV infection, transplant recipients, recipients of corticosteroids or lymphocyte-depleting agents) are at greatest risk of CNS infections from herpes viruses, many of which are inherently neurotropic in their latent state. The herpes viruses most strongly associated with CNS infections include the herpes simplex viruses (HSV-1 and HSV-2), VZV, EBV, CMV, and human herpes virus 6 (HHV-6).

HSV is one of the most common causes of encephalitis, meningitis, and myelitis in both immunocompetent and immunocompromised hosts. Patients with impaired cell-mediated immunity are more likely to develop disseminated disease compared to the immunocompetent host (64). HSV-1 is the most common cause of endemic encephalitis in the United States (15). In the immunocompetent host, HSV-1 encephalitis typically presents as unilateral or bilateral temporal lobe disease. However, clinical manifestations in immunocompromised hosts may be atypical, leading to delays in initiating therapy and to excess mortality (65). Whole-brain irradiation is increasingly recognized as a risk factor for HSV-1 encephalitis (66–68). In contrast, HSV-2 is a relatively infrequent cause of encephalitis but is associated with both meningitis and myelitis (69). HSV DNA detection in the CSF is the gold standard for diagnosis of herpetic neurologic disease. HSV PCR of CSF has a sensitivity approaching 95% and has almost 100% specificity for the diagnosis of encephalitis (70), although false-negative results may be seen early in the course of infection (71).

VZV is a neurotropic herpes virus responsible for the clinical syndromes of chickenpox, seen with acute infection, and for zoster, which occurs with reactivation of latent virus. Immunocompromised hosts, particularly those with impaired cell-mediated immunity, are at the greatest risk of disease (72). CNS VZV infection most commonly manifests as encephalitis, but it can rarely present as varicella cerebellitis, meningitis, myelitis, or vasculopathy (73, 74). CSF examination reveals a mononuclear pleocytosis, and diagnosis is confirmed by detection of VZV via PCR or identification of intrathecal antibodies (75).

EBV is a ubiquitous herpes virus that can cause CNS infection due to acute infection or reactivation of latent virus. Patients with impaired cell-mediated and humoral immunity, including both the HIV and transplant populations, are at particular risk for reactivation disease. Acute EBV infection of the CNS can present as a nonspecific meningitis, encephalitis, or myelitis (76). How-
ever, EBV reactivation may also occur in response to infection with an alternative pathogen, and therefore a positive result should be interpreted with caution (77). For example, in two retrospective studies that characterized the neurologic clinical syndromes associated with positive CSF viral PCR, only 20 to 37% of positive EBV PCR samples were associated with a clinical syndrome consistent with neurologic infection. The remaining 63 to 80% of the positive samples were not associated with viral neurologic infection and were felt to reflect subclinical viral reactivation in the setting of immunosuppression or noninfectious neurologic disease, including malignancy, multiple sclerosis, and stroke. EBV-associated lymphoma is a complication in patients with HIV infection and typically presents as an intracerebral mass lesion. Definitive diagnosis of EBV-associated lymphoma requires hematopathological analysis of a tissue biopsy specimen; however, the finding of an elevated EBV PCR in the spinal fluid may be suggestive of this diagnosis. In particular, EBV CSF viral loads of >10,000 in the setting of a CNS mass lesion has been found to have a specificity of 96% and a positive predictive value of 50% for CNS lymphoma in one small study (78).

CMV is capable of causing both acute primary infection and reactivation disease in patients with impaired cell-mediated immunity, particularly HIV-infected patients. Clinical manifestations in this population include encephalitis, characterized by periventricular white matter changes, and acute lumbosacral myelitis (20, 79). Diagnosis is confirmed by detection of CMV by PCR in the spinal fluid in the setting of a clinically appropriate neurologic syndrome. Much like EBV and HHV-6, CMV can reactivate in the setting of immunosuppression (80).

HHV-6 is a neurotropic herpes virus that has been found to cause encephalitis and myelitis, with a particular propensity to cause neurologic infection in patients following hematopoietic stem cell transplant. HHV-6 establishes latency in both monocytes and brain tissue, and it reactivates in the setting of altered cell-mediated immunity (81). Clinically, its most relevant CNS manifestation is posttransplant acute limbic encephalitis (PALE), marked by anterograde amnesia, seizures, and a mild lymphocytic pleocytosis in the spinal fluid. The highest risk period for this infection is 15 to 60 days following transplantation. Diagnosis is made by the detection of HHV-6 in the spinal fluid by PCR. Detection of HHV-6 must be interpreted cautiously, as HHV-6 DNA has also been found in the spinal fluid of asymptomatic patients due to viral DNA integration into host chromosomes (82). In the absence of viral DNA integration, a positive HHV-6 CSF PCR should only be considered synonymous with CNS infection and not reactivation if a clinical syndrome of encephalitis is present that is not explained by another pathogen.

**Human Immunodeficiency Virus**

HIV infection is frequently complicated by CNS manifestations due to the direct effects of the virus or secondary to opportunistic infections. The most common CNS manifestation of acute HIV infection is aseptic meningitis, which occurs in approximately 10% of symptomatic patients and is characterized by a lymphocytic pleocytosis on CSF analysis in the absence of other pathogens (24, 83). Late in the course of infection, patients may present with AIDS dementia complex, which is characterized by both cognitive impairment and subtle loss of motor control. CSF analysis is typically bland but markers of inflammation are often elevated, including beta-2-microglobulin and neopterin (84). Of note, some HAART drugs are poorly distributed in the CNS, which can lead to the development of drug-resistant HIV quasispecies that can compartmentalize in the CNS. An HIV quantitative viral load that is discordantly high in the CSF when compared to viral load in the serum can diagnose this phenomenon of HIV CNS escape, which has been associated with the development of HIV-associated dementia. In addition to the primary effects of HIV on the central nervous system, profound immunosuppression also predisposes the host to neurologic opportunistic infections that are discussed elsewhere in this chapter, including cryptococcal meningitis, *Toxoplasma* encephalitis, progressive multifocal leukoencephalopathy due to JC virus, and EBV-associated primary CNS lymphoma.

**Human T-Lymphotrophic Virus**

HTLV-1 is a retrovirus that produces a chronic infection of T-lymphocytes and that has a predilection for CD4 cells. Although the majority of infected patients are asymptomatic carriers, approximately 3 to 5% of individuals develop a chronic neuroinflammatory disease known as tropical spastic paraparesis or HTLV-1 associated myelopathy (HAM). HAM has been reported following HTLV infection transmitted through organ transplantation from an infected donor (85). HTLV infects the CNS by the passage of infected leukocytes across the blood–brain barrier. Clinically, HAM presents as spastic paraparesis affecting the lower extremities and as autonomic dysfunction. Detection of HTLV in the serum or CSF by PCR in the appropriate clinical setting is confirmatory (86).
Central Nervous System Infections

JC Virus
JC virus is the etiologic agent of PML, a chronic, demyelinating encephalitis caused by viral reactivation in the CNS. PML is most common in the HIV-infected population, with more than 90% of reported cases occurring in patients with AIDS (87). With the advent of highly active antiretroviral therapies, the incidence of this infection among HIV-infected individuals has decreased, although PML may be seen with initiation of therapy as part of the immune reconstitution inflammatory syndrome. In the last decade, PML has been increasingly diagnosed among patients with autoimmune or oncologic conditions treated with monoclonal antibodies, particularly natalizumab, efalizumab, and rituximab (88). PML causes necrosis of oligodendrocytes and presents with progressive dementia, apraxia, vision changes, and motor deficits. Neuroimaging shows diffuse white matter disease consistent with a demyelinating process. CSF analysis is typically bland, and diagnosis is made by JC virus detection via PCR in the spinal fluid in the appropriate clinical setting (89). The gold standard for diagnosis is the finding of inclusion bodies in the nuclei of affected oligodendrocytes; however, this is rarely obtained due to risks of brain biopsy. BK virus is a less common cause of encephalitis but can occur in immunocompromised patients (90, 91).

Arboviruses
West Nile virus is the most common mosquito-borne pathogen in the United States. While the majority of infected patients remain asymptomatic, up to 20% will develop a febrile illness. Neuroinvasive disease, characterized as meningitis, encephalitis, or myelitis either singly or in combination, develops in <1% of infected individuals but carries a mortality of 10% (92). Severe disease is more common among the elderly, transplant recipients, and patients with lymphoproliferative malignancies. WNV may be transmitted as a donor-derived infection following transplantation (93, 94). Typically, diagnosis is made by serologic detection of West Nile Virus IgM in the spinal fluid, and PCR is less sensitive due to the short duration of detectable virus following infection. The exception is in immunocompromised patients, who may exhibit a delayed serologic response and prolonged detection of virus. Detection of WNV by CSF PCR has been reported more than 100 days after the onset of neurologic symptoms among transplant patients (95, 96).

Enteroviruses
Non-polio enteroviruses are among the most common CNS viral infections and typically present as aseptic meningitis. Patients with impaired humoral immunity are at particular risk for prolonged or chronic meningitis with these agents (97, 98). Diagnosis of CNS infection is made by enteroviral PCR of spinal fluid, with a sensitivity, specificity, positive predictive value, and negative predictive value of 82.1%, 100%, 100%, and 96.2%, respectively (99, 100). Viral culture of CSF has fallen out of favor as a routine diagnostic since it is less sensitive (at only 53 to 75%) and slower than molecular testing.

Other Viruses
A vast number of viral pathogens have been anecdotally associated with CNS infection. These include a multitude of respiratory viruses (e.g., influenza virus, adenovirus, RSV) and gastrointestinal viruses (e.g., rotavirus). Routine CSF PCR for these organisms is not recommended; however, when there are virologic data suggestive of an extra-CNS infection, it is reasonable to perform PCR testing on CSF to establish causality.

Fungal Pathogens
CNS infection with yeasts and molds can present as either meningitis or a focal abscess. Fungal CNS infections represent a significant problem in the immunocompromised host and are associated with significant morbidity and mortality. The risk of infection varies according to type of immunodeficiency and environmental exposure. The majority of these pathogens are acquired through the respiratory tract, with secondary spread to the CNS.

Cryptococcus spp. are important pathogens in the immunocompromised population, particularly in patients with a history of AIDS, solid organ transplantation, hematopoietic stem cell transplantation, or on chronic immunosuppression therapy. In these populations, CNS involvement is identified in 60% of cryptococcal infections (101). Meningoencephalitis is the most common clinical presentation, but mass lesions, termed cryptococcomas, have also been reported. The diagnosis of cryptococcal meningoencephalitis is supported by lumbar puncture with elevated opening pressure and CSF pleocytosis. The sensitivity of the India ink CSF stain is 50 to 75%, whereas lateral flow assay and enzyme immunoassay are highly sensitive in both serum and CSF at 95 to 100% and 90 to 95%, respectively (102–104).

Infections due to the dimorphic endemic fungi, including Histoplasma capsulatum, Blastomyces dermatitidis, and Coccidioides immitis, are relatively frequent in immunocompromised individuals but the incidence...
varies by geographic region. Individuals with defects in cellular immunity such as HIV or those on immunosuppressive medications (particularly tumor necrosis factor alpha inhibitors or calcineurin inhibitors) are more likely to develop disseminated disease. Coccidioidomycosis is generally acquired through the inhalation of spores and is endemic in Mexico, California, and the desert Southwest of the United States. Almost 50% of patients with coccidioidomycosis will have CNS involvement. This is generally in the form of meningitis, but brain abscesses have also been reported. CSF profile can display either a neutrophilic or lymphocytic pleocytosis. Peripheral eosinophilia in a patient with travel to or residence in an endemic region may suggest this diagnosis. CSF culture is insensitive, with cultures positive in only 7 to 30% of cases, and can take upwards of a week to grow. Coccidioides spp. are a laboratory hazard and require biosafety level 2 procedures with a negative air pressure environment. Antibody detection can be performed on both blood and CSF via immunodiffusion, complement fixation, or enzyme immunoassay, with sensitivities ranging from 59 to 80%. Enzyme immunoassay testing, while more sensitive than complement fixation or immunodiffusion, has higher rates of false positivity and should be interpreted based on clinical context. Coccidioides urine and serum antigen testing has been shown to be useful in the diagnosis of severe pulmonary and disseminated infection. A recent study demonstrated that Coccidioides antigen testing had a sensitivity of 93% and a specificity of 100% in 36 at-risk patients.

CNS involvement with histoplasmosis and blastomycosis is less common, even among immunocompromised patients with significant disease burden. Both of these fungi are endemic to the Ohio and Mississippi River valleys in the southeast and midwest United States. CNS infection is seen in approximately 10 to 30% of patients with disseminated blastomycosis and can present as meningitis or as an intracranial or epidural abscess. Laboratory findings supporting the diagnosis of CNS blastomycosis include detection of Blastomyces antigen from CSF, urine, or blood in the appropriate clinical context; sensitivity from urine and serum is about 90%, but there are limited data on the performance of the CSF antigen. Serologic testing is often unhelpful in this difficult diagnosis, as historically sensitivity is poor (9 to 77%) and there is a high incidence of crossreactivity. The growth of organism from CSF is diagnostic but only occurs in 10 to 20% of cases. In many cases, culture of extra-CNS sites such as skin or respiratory specimens is diagnostic.

The incidence of CNS involvement with histoplasmosis is approximately 5 to 20%. Meningitis is the most common clinical syndrome but can be difficult to diagnose. Fungal staining of CSF is low yield and cultures are positive in only ~65% of cases. CSF antigen or antibody testing may be suggestive of meningeal infection, particularly if the titer is higher in CSF than in serum. The antigen crossreacts with other fungal organisms, including Blastomyces spp., and therefore this test is not specific for Histoplasma infection. Positive serology for histoplasmosis or antigen from serum or urine also supports the diagnosis if the clinical presentation is consistent with CNS infection.

Mold infections can involve the CNS through local invasion from the sinuses or from disseminated hematologic spread. Aspergillus spp. are the most common opportunistic infections caused by filamentous fungi, with risk factors including prolonged neutropenia, particularly following hematopoietic stem cell transplant), high-dose steroids or other immunosuppressive agents. CNS involvement occurs in 10 to 20% of cases of invasive aspergillosis and usually presents as a focal abscess extending from the paranasal sinuses, with cases of meningitis rarely described. Suspicion for cerebral aspergillosis is an indication for neurosurgical consultation, as surgical debridement is often needed for both diagnostic and therapeutic reasons. Serum galactomannan is an ELISA test for a cell wall polysaccharide of Aspergillus spp., and a positive test supports, but does not confirm, the diagnosis of aspergillosis in the appropriate clinical setting. False positives can be caused by colonization or infection with other fungal organisms or with the use of beta lactamase inhibitors. Galactomannan testing on the CSF can be performed, but the appropriate diagnostic cutoff value is uncertain. PCR testing for Aspergillosis is now commercially available for blood and bronchoscopy specimens with sensitivities of 50 to 80%, and some studies suggest using PCR in combination with galactomannan for earlier diagnosis and improved accuracy. Individual institutions using laboratory-developed molecular testing on CSF have reported promising results, but more studies are needed to determine the usefulness of this test.

The recognized risk of infection with Aspergillus spp. in the solid organ and hematopoietic stem cell transplant populations has led to the standard use of extended-spectrum azoles or echinocandins for fungal prophylaxis. This intervention has decreased the incidence of posttransplant Aspergillus infections but has resulted in a relative increase in the risk of developing other myce-
lial infections with organisms such as zygomycetes, phaeohyphomycetes or non-Aspergillus hyalohyphomycetes (Scedosporium apiospermum and Fusarium spp.) (123). These infections have a high rate of morbidity and mortality, with diagnosis typically requiring histopathologic examination or culture. The beta-d-glucan (BDG) assay, also known as Fungitell, can sometimes be useful in the evaluation of suspected invasive fungal infection. BDG is a polysaccharide component detectable in the serum of patients with invasive fungal infections, most commonly due to Aspergillus or Candida spp. with a sensitivity of 70 to 80% and specificity of 60 to 80% (124, 125). This test is not specific for a particular organism, so additional workup and testing is typically needed. Infectious due to Zygomyces, Cryptococcus, and Blastomyces spp. generally have a negative BDG assay. Higher levels of BDG in CSF compared to serum are suggestive of invasive fungal infection of the CNS.

**PROTOZOAN PATHOGENS**

Parasitic CNS infection may occur in the immunocompromised host, with the highest incidence in patients with AIDS and significantly depressed CD4 counts (<200 cells/mm³) and in transplant recipients within the first 6 months after transplantation. CNS parasitic infections typically present with focal neurologic deficits due to mass lesions or with meningeal symptoms and altered mental status from parasitic meningoencephalitis. Peripheral eosinophilia, a common finding with many parasitic infections, is frequently absent in the setting of immunosuppression.

The most common CNS protozoan infection in the immunocompromised host is Toxoplasma gondii, which can produce a meningoencephalitis or diffuse cerebral abscesses. Active infection in the immunocompromised host typically develops by one of two routes: 1) reactivation of dormant cysts, or 2) acute donor-derived infection following transplantation of a seropositive donor organ into aseronegative recipient (126, 127). Within the HIV population, toxoplasma encephalitis usually develops by the former mechanism and occurs almost exclusively among patients with CD4 counts <100 cells/mm³. Among transplant recipients, donor-derived infection is greatest among mismatched cardiac transplant and allogeneic stem cell transplant recipients, and pretransplant screening is often performed with consideration for prophylaxis in at-risk individuals (128). CNS toxoplasmosis presents similarly within both patient populations with a combination of fever, headaches, altered mental status, focal neurologic deficits, and seizures. The diagnosis of toxoplasma encephalitis should be considered when ring-enhancing mass lesions are seen on neuroimaging in the appropriate host with a history of seropositivity. Definitive diagnosis is made by the identification of tachyzoites in brain tissue or the growth of the organism in brain tissue culture; however, these gold-standard diagnostics are infrequently obtained due to the high risk of morbidity and mortality with brain biopsy. A positive CSF PCR for *T. gondii* is highly suggestive of toxoplasma encephalitis, with a sensitivity of 87% when performed in CSF samples which were collected up to the seventh day of specific toxoplasmosis treatment (129, 130). Of note, the specificity is variable for serum and CSF antibody testing, in particular since the IgM test can remain positive for months or years following acute infection (131), and clinical suspicion should always guide the interpretation of these diagnostic tests.

Other protozoan pathogens, such as Trypanosoma cruzi and Taenia solium, may cause CNS mass lesions in immunocompromised hosts with a history of travel to Central or South America. Chagas disease affecting the CNS is most common among solid-organ transplantation recipients (due to recipient reactivation or donor-derived infection with *T. cruzi*) and AIDS patients (CD4 counts <200 cells/mm³). Definitive diagnosis is made by detection of intracellular trypomastigotes in the spinal fluid (Fig. 1 and 2), but microscopy has limited sensitivity. In the absence of visualized protozoa, the diagnosis is suggested by the detection of IgG antibodies (with a sensitivity of 93 to 100% in the serum using one of the standard assays) to *T. cruzi* in a patient with characteristic ring-enhancing intracerebral masses (132). Similarly, neurocysticercosis is an infrequent cause of CNS mass lesions in the immunocompromised host with a history of travel to endemic areas. Definitive diagnosis is made by either the visualization of a scolex within a cystic lesion on neuroimaging or histopathologic diagnosis made by biopsy. Alternatively, a presumptive diagnosis can be made by correlating appropriate neuroimaging findings with positive serum or CSF serology for *T. solium*, although, notably, the latter is positive in only 50% of patients with biopsy-proven neurocysticercosis (132).

Parasites are infrequent causes of meningoencephalitis in the immunocompetent host but may be more commonly identified in immunocompromised patients. For example, Strongyloides stercoralis may cause disseminated CNS disease in AIDS patients with CD4 counts...
**FIGURE 1** *Trypanosoma cruzi* meningoencephalitis in a patient with acquired immunodeficiency syndrome. Case published as reference 173.

**FIGURE 2** (A) *Trypanosoma cruzi* trypomastigote in CSF stained with Giemsa. Image courtesy of CDC Division of Parasitic Diseases and Malaria, DPDx. [http://www.cdc.gov/dpdx/trypanosomiasisamerican/gallery.html#tcruzicsf](http://www.cdc.gov/dpdx/trypanosomiasisamerican/gallery.html#tcruzicsf) (B) *Trypanosoma cruzi* trypomastigote in cerebrospinal fluid (CSF) stained with Giemsa. Image courtesy of CDC Division of Parasitic Diseases and Malaria, DPDx. [http://www.cdc.gov/dpdx/trypanosomiasisamerican/gallery.html#tcruzi](http://www.cdc.gov/dpdx/trypanosomiasisamerican/gallery.html#tcruzi)
<200 cells/mm³ and in transplant recipients from endemic tropical regions (53). Definitive diagnosis is made by detection of larvae in the CSF and is suggested by the detection of antibodies to S. stercoralis. Serologic testing does not distinguish between past and current infection and is further limited by cross-reaction with other parasitic infections. Other protozoa that infrequently cause acute meningoencephalitis in the immunocompromised host include Naegleria fowleri, Angiostrongylus cantonensis, Acanthamoeba species, and Microsporidium (with Trachipleistophora species being most associated with meningoencephalitis). Definitive diagnosis necessitates identification of the organism within the spinal fluid or in samples of brain tissue (133).

MYCOBACTERIAL PATHOGENS
Infections with Mycobacterium tuberculosis involve the CNS in approximately 1% of cases and are associated with significant mortality and adverse neurologic outcomes. The highest risk is in individuals with HIV, but CNS tuberculosis also occurs in patients with impaired cellular immunity, including solid organ transplant recipients. The incidence of tuberculosis is much higher in the developing world, and infections can reactivate in immigrants from endemic regions even after many years. Tuberculosis (TB) of the CNS can present as a tuberculoma, abscess, or meningitis. Meningitis is the most common manifestation, and CSF analysis typically features elevated protein, hypoglycorrhachia, and a lymphocytic pleocytosis (134). The diagnosis may be confirmed by positive acid-fast bacilli staining (sensitivity ~25%), CSF mycobacterial culture (sensitivity 70 to 80%) or CSF PCR for M. tuberculosis (sensitivity ~55%) (135). A tuberculoma is a granulomatous lesion with surrounding edema, which typically appears as ring-enhancing on MRI. This is differentiated from a tuberculous abscess by the insidious onset of symptoms, whereas the latter infection presents more acutely and can resemble a bacterial abscess on CNS imaging. Diagnosis of tuberculoma or tuberculous abscess is typically more difficult than TB meningitis as lumbar puncture is often contraindicated due to elevated intracerebral pressure. Presumptive diagnosis can be made in patients with confirmation of TB outside the CNS with appropriate clinical and radiographic features and evidence of latent infection by TB skin test or interferon gamma release assay. However, in cases where there is diagnostic uncertainty, meningeal or brain biopsy may be required to establish the diagnosis (136, 137).

LABORATORY TESTING AND INTERPRETATION
Non-Microbiologic Diagnostic Approaches
Laboratory testing
All immunocompromised patients presenting with concern for CNS disease require routine laboratory testing, including complete blood count with differential, comprehensive metabolic panel, and urinalysis. Abnormal results may provide clues to guide diagnostic testing. For instance, lymphopenia, thrombocytopenia, and increased liver transaminase enzyme levels in a patient from an endemic area during the appropriate season (spring through fall) are suggestive of a rickettsial infection and would prompt initiation of empiric therapy and confirmatory testing (56, 57). These routine tests also are crucial for assessing the potential for adverse effects with empiric or directed antimicrobial therapy. For instance, the finding of an elevated creatinine at presentation might necessitate dose modification of antimicrobial agents.

Neuroimaging
Immunocompromised patients presenting with signs or symptoms of CNS disease should have emergent neuroimaging to assist in defining the disease process and to determine the safety of lumbar puncture. While MRI is more sensitive than CT scan for characterizing parenchymal disease, it may be less readily available than CT and may result in significant delay in the evaluation (13). Therefore, when time is of the essence, such as with acute meningitis, a noncontrast CT scan is an appropriate initial screening test to exclude a CNS mass lesion or other contraindication to lumbar puncture (10). When the diagnosis remains obscure despite initial lumbar puncture results, or when there are focal findings on the neurologic exam, proceeding with brain MRI is appropriate, as radiographic findings often guide appropriate diagnostic testing (18). For instance, the presence of a ring-enhancing intracerebral mass lesion in a patient with AIDS is most suggestive of either toxoplasmosis or primary CNS lymphoma. Definitive diagnosis requires pathologic tissue review; however, this carries risks associated with an invasive surgical procedure. Many experts would therefore recommend additional testing with toxoplasma serology and CSF PCR, and if these supported a diagnosis of toxoplasma encephalitis, empiric treatment should be initiated (138). In cases without laboratory evidence of toxoplasma infection, or that do not respond to empiric therapy, proceeding with brain biopsy is appropriate.
Microbiologic Diagnostic Approaches

Technologic advances in microbiology, immunology, and molecular biology have significantly expanded and improved the capabilities of diagnostic microbiology for CNS infections. The sensitivity of various microbiologic tests varies based on both the specific pathogen and the anatomic location of infection. CNS infections can be confirmed in multiple ways: (a) by cultivation of microorganisms, (b) by direct microscopic examination, (c) by measurement of microorganism-specific immune responses, and (d) by detection of microorganism-specific macromolecules, including both antigens and nucleic acids (18, 139, 140). These techniques are summarized in Table 4.

While in many cases direct testing of material from the CNS, such as CSF or brain tissue, is necessary for diagnosis, ancillary testing on more readily available specimens may be useful as well. For instance, a positive urine antigen for Coccidioides in an immunocompromised patient with meningitis who lived in the southwestern United States would provide strong indirect evidence of coccidioidal meningitis. Similarly, a positive PPD test or interferon gamma release assay in an HIV-infected patient with a ring-enhancing brain lesion would be suggestive (although not definitive) of an M. tuberculosis brain abscess. Extraneural sites of infection should be aggressively sought to identify areas amenable to biopsy. In particular, for fungal, mycobacterial, and Nocardia infections, chest imaging may disclose a pulmonary site of infection that is amenable to diagnostic bronchoscopy, potentially sparing the patient an invasive neurosurgical procedure.

CSF Sample Collection and Processing

All immunocompromised patients with concern for neurologic infection and no contraindication to lumbar puncture should have expedited CSF analysis. Standard testing should include cell count and differential, glucose, and protein, as well as stains and cultures for bacteria, fungi, and mycobacteria (40). Neutropenic patients with bacterial meningitis may have normal cell counts, making the diagnosis in this population particularly challenging (9).

Prompt and appropriate sample collection, transport, and processing are important to maximize specimen integrity. Ideally, CSF for microbiologic studies should be placed in separate containers from that needed for other testing to expedite processing and to minimize contamination. CSF specimens should be delivered to the laboratory immediately after lumbar puncture, as concentrations of CSF neutrophils degrade by up to 50% one hour post-lumbar puncture (141). If not rapidly processed, CSF should be incubated at 35°C or left at room temperature. The exception to this rule involves CSF for viral culture and molecular tests. These specimens may be refrigerated for less than 24 hours after collection or frozen at −80°C if a longer delay is anticipated.

The yield of fungal and mycobacterial stains and cultures is improved with a larger volume of CSF (10 to 20 ml) (134). Larger volumes (e.g., >10 cc) are also indicated if there is concern for primary CNS lymphoma or other malignancy, as the sensitivity of cytologic examination correlates with volume of sample. Multiple samples may be required to make a diagnosis. For instance, the sensitivity of CSF smear and culture for M. tuberculosis increases from 37% to 87% when four sequential examinations of CSF are performed (142).

Direct Microscopic Examination

Although there is no single laboratory test of CSF that reliably distinguishes between bacterial and viral pathogens, a positive Gram stain is virtually 100% diagnostic of bacterial meningitis, with a specificity greater than 99% (143, 144). Microscopic examination of a

### TABLE 4 Microbiological methods used for laboratory diagnosis of CNS infections

<table>
<thead>
<tr>
<th>Test</th>
<th>Turnaround time</th>
<th>Positive result interpretation</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct examination</td>
<td>1–3 h</td>
<td>Highly suggestive</td>
<td>Rapid</td>
<td>Poor sensitivity; false positives may occur.</td>
</tr>
<tr>
<td>Culture</td>
<td>2–42 days</td>
<td>Definite</td>
<td>Allows drug susceptibility testing</td>
<td>Time-consuming; poor sensitivity; not all microorganisms are culturable; may be affected by prior antimicrobial use.</td>
</tr>
<tr>
<td>Serology</td>
<td>4–6 h</td>
<td>Indirect</td>
<td>Automated</td>
<td>Results are generally retrospective; immunocompromised host may be unable to mount a response; nonspecific cross-reaction.</td>
</tr>
<tr>
<td>Molecular diagnostics</td>
<td>1–2 days</td>
<td>Highly suggestive</td>
<td>High sensitivity and specificity</td>
<td>False-positive results may be seen due to carryover contamination; false-negative results may occur due to inhibitors in specimen; specimen integrity and processing important in maximizing results.</td>
</tr>
</tbody>
</table>
Gram-stained smear of CSF sediment obtained after cytocentrifugation provides a rapid and accurate identification of the causative microorganism in up to 90% of untreated patients with bacterial meningitis, although the sensitivity varies based on bacterial burden and type of organism (143, 145). Rapid diagnosis may occasionally be made by microscopy using acid-fast bacilli stain, modified acid-fast bacilli stain, darkfield examination, wet mount, and India ink stain. Amoebae are best observed by examining CSF sediment as a wet preparation under phase-contrast microscopy.

**CSF Antigen Testing**

Bacterial antigen testing in CSF is of limited utility given the low sensitivity of these assays (145, 146). An exception is the immunochromatographic test for *S. pneumoniae* (Binax NOW Streptococcus pneumoniae test; Binax Inc., Portland, ME), which has excellent specificity and specificity for the diagnosis of pneumococcal meningitis (147).

In contrast to the limited utility of antigen testing for the diagnosis of bacterial infections, these tests play an important role in detection of fungal infections of the CNS. Detection of cryptococcal antigen in either the CSF or serum of patients with HIV/AIDS is highly sensitive, and high antigen levels may correlate with mortality (148, 149). However, capsule-deficient strains of *C. neoformans* would not be detected through antigen assays (150). Detection of *Aspergillus* galactomannan antigen in the cerebrospinal fluid is suggestive of cerebral aspergillosis and serves as a marker of therapeutic response (151, 152). *Histoplasma* antigen testing of CSF has a sensitivity ranging from 38 to 67%, with a CSF-to-urine ratio of >1 suggestive of intrathecal antigen production (117).

A serum assay to detect BDG is FDA-approved for the diagnosis of invasive fungal infection. BDG is a highly conserved component of the fungal polysaccharide cell wall, with the exception of Mucorales and Cryptococcus. This assay has been best studied in the detection of invasive *Aspergillus* or *Candida* infections, with a sensitivity of 67 to 84% and a specificity of 80 to 90% (125). There are increasing data to suggest elevated CSF BDG may be useful in the diagnosis of CNS fungal infections. Elevated CSF BDG levels have been reported in fungal meningitis related to an outbreak from contaminated methylprednisolone injections (153) and in pediatric patients with *Aspergillus* or *Candida* meningitis (154). An elevated ratio of CSF-to-serum BDG is suggestive of CNS infection (155). Interestingly, a number of reports have detected elevated levels of BDG in the CSF of patients with cryptococcal meningitis, despite the fact that BDG is a minor component of the cell wall for this organism (155, 156).

**Culture**

CSF culture remains an important diagnostic modality for detection of many bacterial, mycobacterial, and fungal causes of meningitis, and it allows susceptibility testing on cultured organisms. The yield of CSF culture in bacterial meningitis is >75% in the untreated patient (145, 146). A limitation of culture is the relatively slow rate of growth, particularly for fungal and mycobacterial organisms, which may lead to a significant delay in diagnosis. While the phenotypic techniques used for antimicrobial susceptibility testing of CNS infections remain the same, criteria for determining antibiotic resistance can differ from those used for other sites of infection. Penicillin minimal inhibitory concentration breakpoints for pneumococcal CNS isolates, for example, are higher than those used for non-CNS isolates, due to the lower bioavailability of the antibiotic in reaching the CNS (157). Viral culture of CSF is of limited utility and is not recommended as part of the routine evaluation for patients with CNS infection (13, 17, 18), although results may have implications for outbreak investigations and epidemiologic surveillance (158).

**Serology**

Serology has a limited role in the diagnosis of viral CNS infection. Local production of HSV IgG antibodies in CSF can be used in diagnosis; however, the presence of antibody is delayed until day 10 or 12 of infection and therefore is of limited clinical utility (159). A significant limitation in the use of serology for the diagnosis of CNS infection is that a positive antibody result may reflect an extraneurologic site of infection or may represent a prior infection. An exception is West Nile virus infection wherein detection of CSF IgM is the most sensitive diagnostic test for neuroinvasive WNV disease (92, 160). Immunocompromised patients may have delayed or blunted serologic responses to infection, which may decrease the sensitivity of antibody detection for diagnosis of neuroinvasive WNV disease (93).

Neurosyphilis should be considered in a patient with laboratory evidence of syphilis and focal neurologic findings. A reactive CSF venereal disease research laboratory (VDRL), a nontreponemal test, is considered diagnostic but is insensitive. In cases with a high suspicion for neurosyphilis despite a negative CSF VDRL, a specific treponemal test of CSF, such as the fluorescent treponemal antibody absorption test, is indicated. The fluo-
resent treponemal antibody absorption test is highly sensitive but is less specific than the VDRL. The diagnosis of neurosyphilis is particularly challenging in patients with HIV, with some experts recommending treatment for patients with a pleocytosis of >20 WBC/mm\(^3\) and no alternative diagnosis, irrespective of the results of CSF syphilis assays (55, 161).

To differentiate between peripheral and CNS infections, antibody titers in serum and CSF can be measured in parallel. With a peripheral infection, the antibody titer in the CSF should be less than that of the peripheral blood, due to the protective effect of the BBB. Antibody titers in CSF higher than those found in serum are suggestive of intrathecal antibody synthesis. Peripheral blood contamination of CSF at the time of lumbar puncture or BBB inflammation may skew this ratio. Examples of CNS infections where intrathecal antibody index may be useful for diagnosis include Borrelia burgdorferi and VZV meningoencephalitis (74, 162).

Molecular Assays

Historically, identification of a microbiologic agent causing CNS infection has been hindered by the low yield of CSF viral culture, delay in host production of organism-specific antibodies, and morbidity associated with brain biopsy. With the advent of molecular diagnostic clinical laboratory procedures, it is now possible to diagnose viral etiologies rapidly and with high sensitivity and specificity. PCR has become the primary diagnostic modality for detection of CNS infections due to herpesviruses and enteroviruses (80, 163, 164). PCR amplification of viral nucleic acid in the CSF offers superior test characteristics to culture-based methods, and test turnaround time has been significantly shortened to just a few hours by incorporating either colorimetric enzyme immunoassay or real-time detection methods (165). Because of the large number of organisms that have been associated with CNS infections, particularly in the immunocompromised host, there has been interest in the use of multiplex panels capable of testing for a number of neuropathogenic organisms simultaneously (166). A challenge is the interpretation of detection of organisms that may latently infect neurons or leukocytes, such as EBV or HHV-6 (167). Quantitative PCR may be helpful in this regard, as higher viral loads in CSF compared to serum might be suggestive of neuroinvasive disease (78, 168).

In addition to the proven superiority of PCR for detection of herpesviruses and enteroviruses, molecular testing is increasingly recognized as the test modality of choice for other important viruses in the immunocompromised population. Detection of JC virus in the CSF by PCR allows noninvasive diagnosis of PML in many patients (169). In immunocompromised patients, WNV PCR of CSF may be superior to serology, due to delayed production of antibodies (93, 95). Despite the many advantages of nucleic acid amplification testing, results must be interpreted with caution given the possibility of false-positive results due to contamination or the detection of latent virus (170). One large study identified the positive predictive value for CMV and EBV amplified in CSF as 29% and 37%, respectively (171). Interpretation of a positive PCR result requires consideration of the clinical presentation and in some cases may be aided by quantitative PCR, detection of lytic-cycle mRNA, or detection of viral transcripts indicative of replicating virus (77, 78, 172).

Diagnostic Evaluation

The differential diagnosis of CNS infections in the immunocompromised host is very broad, and appropriate and cost-effective diagnostic testing should be guided by the acuity of presentation, type and degree of immunocompromise, serostatus of the recipient and donor for organ transplants, use of prophylactic medications, and epidemiologic factors. The most common infectious agents causing meningitis, encephalitis, and myelitis among immunocompromised patients, and their diagnostic methods, are listed in Tables 1, 2, and 3. Detailed discussion of the specific laboratory diagnostic modalities is provided in the organism-specific chapters.

CNS infections remain important causes of morbidity and mortality in immunocompromised hosts and present a particular challenge for the clinician and microbiologist. While this chapter outlines many of the most common etiologic agents, with the emergence of new infections, the migration of infectious agents into new geographic niches, and the advent of an increasing array of medications with suppressive effects on the immune system, the field continues to evolve. Challenges for both the clinician and the clinical microbiologist are to optimize existing testing and to develop newer diagnostic techniques to keep pace with this rapidly expanding field.

REFERENCES


