CNS Infections in Solid Organ Transplant Recipients

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INTRODUCTION

With advances in medical care, the number of immunosuppressed patients increases annually, particularly the number of solid organ transplant recipients. Whereas end-organ dysfunction was once a death sentence, solid organ transplantation now offers a life-saving option to tens of thousands of patients each year.

In 2004, more than 27,000 solid organ transplants were performed, including 16,000 kidney, 6168 liver, 2016 heart, 1172 lung, 880 kidney-pancreas, 604 pancreas, 146 intestine, and 39 heart/lung transplants.1 Rapid growth in the use of solid organ transplantation has necessarily led to advances in the care of patients receiving transplants, which in turn has allowed for increased patient and graft survival. For example, the reported 3-year patient survival rates after transplantation between July 1999 and December 2001 were 87.61% for deceased donor kidney recipients, 93.98% for living donor kidney recipients, 78.19% for deceased donor liver recipients, 77.3% for living donor liver recipients, 61.17% for lung recipients, and 55.7% for heart recipients.2

With greater understanding of the clinical care needs of transplant recipients have come important lessons about potential complications of organ transplantation. These include iatrogenic complications (eg, surgical misadventures, side effects of immunosuppressive agents), exacerbation of underlying medical illness by antirejection therapy (eg, worsening diabetic control from corticosteroids, hypertension from calcineurin inhibitors), and new or unusual manifestations of disease (eg, post-transplant lymphoproliferative disease, transplant-associated infection). Indeed, each year new information is revealed about unusual clinical presentations of bacterial, viral, and fungal pathogens in recipients of solid organ transplants. Another consequence of the increase in solid organ transplantation is that medical care for transplant recipients is no longer reserved for specialized centers. The prevalence of patients with solid organ transplants mandates that all clinicians acquire the knowledge and skills needed to properly care for these patients.

Neurologic complications are estimated to occur in 30% to 60% of patients after solid organ transplantation.3–5 Of these, infections of the central nervous system (CNS) are seen in 5% to 10%.6 The significant morbidity and mortality from CNS infections in the solid organ transplant recipient make it important that all neurologists be able to diagnose these infections early in the disease course and understand when special methods for detection and isolation are needed. CNS infections can be a difficult clinical problem in the immunosuppressed transplant recipient, and the large differential diagnosis in this setting can at times seem daunting. The effects of immunosuppressive medications used after transplantation not only increase susceptibility to infection but also change the presentation and diagnosis of the infection. However, a systematic approach allows rapid narrowing to likely pathogens and facilitates expeditious and accurate diagnosis.

RISK OF CNS INFECTION IN TRANSPLANT RECIPIENTS

FACTORS INCREASING RISK OF INFECTION

Immunosuppression

Immunosuppression was first used in transplantation in 1964 and was a combination of azathioprine and corticosteroids. At that time, 1-year renal allograft survival rates were less than 60%.7 It was not until more than a decade later, in 1978, that cyclosporine was used for immunosuppression in solid organ transplant recipients. Acute rejection rates and 1-year graft outcomes have improved significantly since the introduction of cyclosporine.8 In the last 20 years, several new immunosuppressive agents and combination therapies have been used in the induction and maintenance of transplant immunosuppression and the treatment of rejection.

Newer immunosuppressive agents have dramatically reduced the rates of acute graft rejection but also...
appear to have exacerbated the problem of post-transplantation infections. For example, infection now exceeds rejection as the precipitating factor in hospitalization of patients in the first 2 years after a solid organ transplant. Indeed, among patients receiving a transplant in 1987, the rate of hospitalization for rejection exceeded the hospitalization rate for infection in the early (1–6 months) and later (6–24 months) post-transplantation periods. In contrast, among patients who received transplants in 2000, the hospitalization rate for infection was twice that for rejection during both the early and later post-transplantation periods.

It is well known that the intensity of immunosuppression changes the types and manifestations of opportunistic infections. All transplant patients undergo induction immunosuppression, and for those patients who do not ultimately experience graft rejection, induction immunosuppression represents the time of greatest immunocompromise. The period of induction immunosuppression typically begins during the transplant procedure and extends to the days and weeks following successful transplantation. Some newer induction methods call for administration of immunosuppressants, including monoclonal antibodies, before transplantation. In preparation for the intense immune response to the foreign graft, induction of immunosuppression usually includes agents that blunt both B- and T-cell function.

After induction, immunosuppressants are tapered to maintenance levels. Most contemporary maintenance immunosuppression regimens involve 3 agents: a corticosteroid (prednisone, methylprednisolone), a calcineurin inhibitor (cyclosporine, tacrolimus), and a nucleotide synthesis inhibitor (azathioprine, mycophenolate mofetil). Although dose, duration, and temporal sequence of individual agents vary among transplant centers, the level of immunosuppression generally decreases with time in patients with an uncomplicated post-transplantation course. However, in patients who experience graft rejection or infection with an immunomodulating virus, immunosuppression may actually exceed that given in the induction phase. These patients may receive very large doses of corticosteroids, anti-lymphocyte preparations, and/or plasmapheresis to reduce the immune assault on the graft. This treatment places the patient at high risk for infection.

**Epidemiologic Exposures**

Information about a transplant recipient’s epidemiologic exposures is important in determining which CNS infections the patient may be at greatest risk of acquiring. Unfortunately, the donor’s exposures may also be critical to diagnosing the infection. Obviously, epidemiologic risk in the donor is more difficult to discern, and for this reason extensive questioning of donor next of kin and medical evaluation are undertaken prior to organ donation. However, even this extensive preparation sometimes does not reveal an infection that may be transmitted with the donated organ, and retrospective review of the donor medical record may be necessary for deciphering the nature of the CNS process.

Epidemiologic risk in a solid organ transplant recipient is more complex than in the immunocompetent patient. In the setting of intense immunosuppression, the patient with a new organ transplant is at risk from many sources. Examples of recently contacted pathogens (eg, infectious agents in the recipient’s community) that may cause clinically relevant CNS infection include food-borne agents such as *Listeria*. In the patient with a solid organ transplant, contact with *Listeria* is likely to cause symptomatic infection soon after exposure. The transplant recipient is also usually at high risk for infection by nosocomial pathogens. Many transplant patients spend a great deal of time in hospitals and other medical care centers (eg, dialysis centers) prior to and after transplantation and, thus, are at risk for harboring or contacting drug-resistant and difficult to treat pathogens.

Finally, the immunosuppressed patient is at risk for reactivation of infection acquired in the distant past. Exposure to the endemic fungi (eg, *Blastomyces dermatitidis*, *Coccidioides immitis*, *Histoplasma capsulatum*) may cause disease with recent exposure or by reactivation of latent disease from remote exposure. The same holds true for the important CNS pathogen *Mycobacterium tuberculosis*. Although the host’s immune response can hold the pathogens at bay for many years, the immunosuppression required to prevent transplant rejection blunts the immune siege. This decreased immune response amplifies the effects of these infections, increasing the risk of tissue invasion, dissemination, and superinfection.

In the solid organ transplant recipient, infection with endemic fungi or *M. tuberculosis* can result in 3 patterns of disease manifestation: progressive primary infection, reactivation infection, and reinfection. Systemic dissemination is common, and it is usually in this setting that CNS disease is seen. These infections may all present as fever of unknown origin, progressive meningitis, or metastatic infection to such sites as the liver, mucocutaneous surfaces, bones and joints, genitourinary tract, and CNS. As a result, the history must include careful questioning about recent and remote contacts and risk factors. For example, if fungal meningitis is suspected in a patient who has not lived in
California since childhood, *C. immitis* should still be included in the differential diagnosis, as this infection can reactivate in the solid organ transplant recipient many years after initial exposure.

Pretransplantation evaluation can be invaluable for assessing the transplant recipient’s risk of reactivation disease. This evaluation usually includes assessing for tuberculosis risk factors as well as testing for latent tuberculosis; serologic testing for endemic fungal disease and prior exposure to toxoplasmosis; and testing for viral infections such as Epstein-Barr virus (EBV), cytomegalovirus (CMV), herpes simplex virus (HSV), and varicella-zoster virus (VZV). This may also be an ideal time to minimize epidemiologic risk via immunization (while the patient is able to mount a superior immune response prior to intense post-transplantation immunosuppression) and targeted chemoprophylaxis or treatment of latent infection.

**INFECTION PROPHYLAXIS**

Patients routinely receive prophylaxis for opportunistic infection after undergoing solid organ transplantation. The length and nature of prophylaxis varies by patient risk and transplant center. Knowledge of the type of prophylaxis a given patient has received is valuable in the work-up for suspected CNS infection.

The most effective prophylactic therapy is trimethoprim-sulfamethoxazole (TMP-SMX), prescribed as a single-strength tablet containing 80 mg of trimethoprim and 400 mg of sulfamethoxazole and taken daily for the first 4 to 12 months after transplantation. The primary objective of TMP-SMX prophylaxis is to prevent *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) pneumonia, a once-common post-transplantation infection in patients who did not receive prophylaxis. Routine use of TMP-SMX also reduces other typical community-acquired infections (eg, urinary tract infection, urosepsis) as well as upper respiratory infections that may have important CNS implications (eg, sinusitis, otitis). Additionally, TMP-SMX reduces the risk of infection with several other opportunistic CNS pathogens, such as *Listeria monocytogenes*, *Nocardia asteroides*, and *Toxoplasma gondii*. In transplant recipients receiving prophylaxis with TMP-SMX, the incidence of CNS toxoplasmosis is low—similar to that in patients with AIDS who are receiving TMP-SMX prophylaxis.11

Other anti-infective agents are used prophylactically in transplant recipients at highest risk for certain types of infections but are not routinely offered to all patients with a solid organ transplant. Treatment with acyclovir is offered to reduce the risk of infection by HSV, VZV, and EBV.12 Ganciclovir is used for patients at risk for early CMV disease. Antifungal prophylaxis is generally offered only to patients at highest risk for fungal disease, such as high-risk liver transplant recipients.

**CLINICAL APPROACH TO SUSPECTED CNS INFECTION IN TRANSPLANT RECIPIENTS**

**CLINICAL PRESENTATION**

The usual clinical presentation of a CNS infection may be different in a patient with a solid organ transplant than in an immunocompetent patient. As with any patient in transplant recipients, CNS infections may be associated with fever, headache, meningismus, new-onset seizure, altered sensorium, and/or focal neurologic deficit. Because any or all of these manifestations may be subtle or absent as a result of the anti-inflammatory effects of immunosuppressants,13 the threshold should be lower for suspecting CNS infection in the transplant recipient who presents with 1 or more of these symptoms. The most reliable features that suggest CNS infection are unexplained fever with headache.13

**FACTORS THAT NARROW THE DIFFERENTIAL DIAGNOSIS**

Clinicians approaching a transplant recipient with suspected CNS infection are often overwhelmed with the broad differential diagnosis, thinking that the infectious agent “could be anything.” However, several clinical factors significantly narrow the differential diagnosis and are important to understand when assessing such a patient.

**Time Frame of Transplant-Related Infection**

Perhaps the most important factor is timing. The time frame of transplant-related infections is classically defined as early (perioperative period to 1 month post-transplantation), intermediate (1–6 months post-transplantation), or late (> 6 months post-transplantation) (Figure 1). Deviations from the usual sequence of infections after transplantation suggest the presence of unusual epidemiologic exposure or excessive immunosuppression. In times of intensified immunosuppression, such as while undergoing treatment of rejection, the “clock” is reset and the patient is again at increased risk for the same opportunistic pathogens as those seen in the early post-transplantation period.14

**Early post-transplantation period.** It is a generally held concept that early infections are the same as those typically occurring in any postsurgical patient. As such, wound infection, line sepsis, postoperative urinary tract infection, and pneumonia are to be expected in this...
Figure 1. Usual sequence of infections after organ transplantation. Zero indicates the time of transplantation, solid lines indicate the most common period for the onset of infection, and dashed lines indicate periods of continued risk at reduced levels. CMV = cytomegalovirus; EBV = Epstein-Barr virus; HSV = herpes simplex virus; PTLD = post-transplantation lymphoproliferative disease; RSV = respiratory syncytial virus; VZV = varicella-zoster virus. (Adapted with permission from Fishman JA, Rubin RH. Infection in organ-transplant recipients. N Engl J Med 1998;338:1743. Copyright © 1998, Massachusetts Medical Society. All rights reserved.)
Meningitis in the transplant recipient

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Most cases of CNS infection in the early period are caused by common bacterial pathogens (eg, gram-negative bacteria, staphylococcal species), often from dissemination of one of the infectious processes mentioned earlier.2 Nosocomial meningitis, however, is not common, and even postsurgical CNS infection is almost exclusively seen in patients who have undergone a neurosurgical procedure. However, a smaller number of cases of CNS infection in the immediate post-transplantation period have been associated with excess epidemiologic exposure, such as outbreaks of disseminated Aspergillus infection.3

Also in contrast to the general concept, there have been several recent reports of unusual CNS infections transmitted from donor to recipient that bear particular consideration in the early post-transplantation period. Although extremely rare, these infections are noteworthy, and all clinicians should be aware of their potential occurrence. Donor-transmitted CNS infections may be of 2 types: infections that were not symptomatic in the donor but are unusual or unusually severe in the recipient as a direct result of intense induction immunosuppression, and infections that resulted in unrecognized CNS disease, often even the death of the donor. Recent examples include the transmission of lymphocytic choriomeningitis (LCM) virus and West Nile virus encephalitis to organ transplant recipients by infected donors and a tragic case of rabies transmitted to 4 recipients of organs from a single donor (see pages 12 and 13 for further discussion). Any unexpected infectious syndromes in recipients of solid organ or tissue transplants should raise concern about the possibility of transplant-associated transmission of an infectious agent. Providers should alert the associated organ procurement organization, tissue bank, and public health authorities when such events are suspected.

Intermediate post-transplantation period. Most classic opportunistic pathogens are seen during the intermediate period.14 This is also the time when immunomodulating viruses appear and begin to further perturb the host immune response.5 The most prevalent and clinically important virus that alters the immune response is CMV; however, the other human herpesviruses (HHVs) as well as hepatitis viruses and HIV, if active in the early post-transplantation period, can all produce significant CNS as well as immunomodulatory effects.6 Interestingly, these viral infections can also precipitate rejection. Whether immunomodulating viruses are involved at the onset or not, in the 5% to 10% of transplant recipients who experience recurrent or chronic rejection,15 a chain reaction of infections and rejection is often set into motion. Rejection, both acute and chronic, results in greater exposure to immunosuppressive agents, which often facilitates the same chronic and immunomodulating viral infections. Thus begins the downward spiral of infection precipitating more difficult to control rejection, precipitating more difficult to control infection, and so on. The combination of increased immunosuppression and viral infection places a patient at greatest risk for opportunistic infections. These include reactivation of infections previously controlled by the patient’s own immune response as well as new infections by pathogens that would not normally harm a person with an intact immune system in the absence of an excess epidemiologic exposure (eg, L. monocytogenes, N. asteroides, Cryptococcus neoformans, Aspergillus species)10,16

Late post-transplantation period. In most transplant recipients, immunosuppressive therapy is tapered after the first 6 months. This period is generally associated with a decreased risk of opportunistic infection. However, it should be noted that most cases of progressive multifocal leukoencephalopathy (PML) and cryptococcal meningitis occur 6 or more months after solid organ transplantation.11

Clinical Syndrome

Classifying the CNS syndrome also helps to narrow the field of potential pathogens in the transplant recipient with suspected CNS infection (Table). Although many opportunistic agents can cause more than one syndrome, defining the syndrome helps to assign likelihood of a specific pathogen for a given patient based on the constellation of symptoms, risk factors, and preliminary testing. For example, Listeria, Cryptococcus, and Aspergillus account for 90% of the nonviral CNS infections in renal transplant recipients; however, if focal neurologic deficits are present, the etiology is most likely aspergillosis, toxoplasmosis, PML, or a fungal abscess.15

Meningitis. Meningitis in the transplant recipient has 4 distinct types defined by length of symptoms. Each type has a different clinical presentation and different likely etiologic agents. It must be emphasized, however, that many of the expected features of meningitis may be absent or diminished in solid organ transplant recipients as the result of the anti-inflammatory properties of transplantation immunosuppressants.

Acute bacterial meningitis typically presents as rapid evolution of fever, headache, and meningeal signs over the course of hours to days. In transplant recipients, meningitis usually is caused by L. monocytogenes,7 although these patients are still at risk for the conventional culprits, including Streptococcus pneumoniae and Neisseria meningitidis.

Subacute meningitis typically presents as fever and
headache evolving over several days to weeks and is often associated with mental status changes. Although most commonly caused by *C. neoformans*, several other infectious agents also produce subacute meningitis, especially with disseminated infection. These agents include *M. tuberculosis, L. monocytogenes, Histoplasma capsulatum, N. asteroides, Strongyloides stercoralis, Coccidioides immitis, Epstein-Barr virus (EBV)*, *Candida* species.

Chronic meningitis may present as progressive neurocognitive decline and signs and symptoms of meningeal inflammation over weeks to months. *M. tuberculosis, H. capsulatum, N. asteroides, S. stercoralis, C. immitis, EBV*.

Recurrent

Herpes simplex virus

*L. monocytogenes*

Finally, recurrent meningitis may manifest as clearly separate bouts of acute or subacute meningitis with intervening periods of normalcy. Most cases of benign recurrent aseptic meningitis (Mollaret’s meningitis) are caused by HSV, especially HSV-2, although this has not been studied specifically in patients with solid organ transplants. Recurrent meningitis due to bacteria, including *L. monocytogenes*, has also been reported in transplant recipients.

**Progressive neurocognitive decline.** Progressive neurocognitive decline or dementia, with or without focal abnormalities or seizures, may be related to an infectious process in the solid organ transplant recipient. As noted, some cases are secondary to chronic meningitis. Progressive neurologic decline may also be
related to an accelerated medical illness seen after transplantation. For example, steroid-induced diabetes and hypertension predispose the transplant recipient to premature cerebral vascular disease or occasionally to demyelination or other toxic effects of immunosuppressive medications such as cyclosporine or tacrolimus. The most classically associated infection causing this clinical syndrome is PML due to the JC virus, a polyomavirus. However, progressive neurologic decline may be the result of other viral infections, including HSV, CMV, EBV, and HIV infection.

**Abscess.** Focal CNS lesions may be infectious or noninfectious. Focal brain infections, often presenting as seizures or focal neurologic abnormalities, have been documented in 0.36% to 1% of solid organ transplant recipients. It should be noted, however, that unlike immunocompetent patients with a brain abscess, patients who are receiving transplantation immunosuppressants may not show evidence of a focal neurologic defect and may present with only headache, fever, or altered cognition. Aspergillus species are the most frequent causes of post-transplantation brain abscess. Toxoplasma, Cryptococcus, Nocardia, L. monocytogenes, and M. tuberculosis can also produce brain abscess. Aside from those atypical bacteria just mentioned, bacteria are only infrequently associated with brain abscess in transplant recipients.

**Transplanted Organ**

Finally, the specific organ that is transplanted can influence the nature of infection in the transplant recipient. Not all organs require the same depth of immunosuppression. For example, a lung transplantation requires more intense immunosuppression than a renal transplantation. Also, certain organs appear to be more susceptible to infection by specific pathogens after transplantation. For example, there is an association of T. gondii infection with heart transplantation, Aspergillus infection with lung transplantation, C. neoformans infection with liver transplantation, and resistant gram-negative infections with renal transplantation.

**DIAGNOSTIC EVALUATION**

The diagnostic evaluation of the transplant recipient with a suspected CNS infection must expeditiously pursue a definitive diagnosis, as the sequelae may be serious and the risk of a poor outcome increases with time. The work-up should include sophisticated neuroimaging (eg, magnetic resonance imaging [MRI], computed tomography [CT], with and without a contrast agent if at all possible. If signs and symptoms of infection are present (eg, new-onset headache, fever, mental status change) or if symptoms are not explained by imaging findings, a lumbar puncture should be performed if no contraindication exists.

Cerebrospinal fluid (CSF) evaluation should include cell count/differential, glucose, protein, Gram stain, and bacterial culture in all patients. Other testing should be dictated by the clinical presentation, the phase of immunosuppression, and other clinical criteria previously discussed. Depending on the clinical circumstances, fungal staining and culture, Ziehl-Nielsen acid-fast staining and mycobacterial culture, VDRL (Venereal Disease Research Laboratories) testing, cryptococcal antigen (CrAg) testing, West Nile IgM, and polymerase chain reaction (PCR) assay (for HSV, EBV, CMV, VZV, HHV-6, measles virus, BK virus/JC virus, or M. tuberculosis) may be diagnostic.

Occasionally, a diagnosis cannot be made via noninvasive or minimally invasive tests. Brain biopsy may be required for a definitive diagnosis. In most cases, biopsy can be made less invasive using a stereotactic technique. If CNS herniation is imminent or the tempo of disease progression is very rapid, open biopsy with surgical decompression may be preferred. Because most focal CNS infections in transplant recipients are secondary to disseminated processes, cultures from other tissues (eg, skin, lung, solid organ), pulmonary secretions (eg, sputum, bronchoalveolar lavage fluid, chest tube drainage), or the blood may afford a diagnosis without the need for brain biopsy.

**AGENTS OF CNS INFECTION IN TRANSPLANT RECIPIENTS**

**TYPICAL BACTERIA**

Patients with solid organ transplants are at risk for bacterial meningitis, which may be secondary to a number of agents.

**Listeria monocytogenes**

Although an infrequent cause of illness in immunocompetent persons, L. monocytogenes is an important cause of life-threatening infections, including sepsis and meningoencephalitis, in solid organ transplant recipients. L. monocytogenes has tropism for the brain and the meninges. Infection with L. monocytogenes often results in a diarrheal illness followed by meningitis in the solid organ transplant recipient.

**Clinical presentation and diagnosis.** Meningitis is the most common manifestation of L. monocytogenes infection, although meningoencephalitis, rhombencephalitis
(encephalitis involving the brainstem), cerebritis, and CNS abscess formation also may occur. The onset of infection may be acute or subacute. The clinical picture may include high fever, nuchal rigidity, movement disorders (eg, tremor, ataxia), and seizures. Indeed, seizures are seen more commonly in meningitis caused by Listeria than in other types of meningitis. Patients with listerial meningoencephalitis have subacute onset of symptoms, which often include focal neurologic findings in the hindbrain (eg, ataxia) and may include multiple cranial nerve abnormalities. Fever may be absent or go unnoticed in 15% of cases. CSF analysis may show a negative Gram stain. Additionally, the Gram stain may be initially misread as pneumococcal infection. There is often a pleocytosis and an elevated protein but a normal glucose concentration. Blood cultures are usually positive before the CSF culture.

Treatment. Treatment of transplant recipients with suspected bacterial meningitis should always cover drug-resistant pneumococci, N. meningitidis, and L. monocytogenes. A combination of 3 drugs, such as vancomycin, ceftriaxone, and high-dose ampicillin, are often given until cultures and susceptibility panels return. A relapse rate of 35% is reported in transplant patients with listerial meningitis and/or bacteremia who are treated for less than 3 weeks; high-dose penicillin or ampicillin therapy for 4 to 6 weeks is recommended for this patient group.

Streptococcus pneumoniae

Organ transplant recipients are at increased risk for developing invasive pneumococcal disease, the incidence of which has been calculated at 36 per 1000 patient-years for recipients of heart transplants and 28 per 1000 patient-years for recipients of kidney transplants—rates that exceed the estimated incidence of invasive pneumococcal disease in the general population. Interestingly, despite an excess of cases of disseminated pneumococcal disease in transplant recipients, most of these infections were actually blood stream infections; pneumococcal meningitis is rarely seen in solid organ transplant recipients. Infections with S. pneumoniae usually occur at least 3 months after transplantation. Many transplant patients harbor some of the known risk factors for drug-resistant pneumococci, such as recent antibiotic use. This should be kept in mind when prescribing antimicrobial therapy for suspected pneumococcal meningitis.

Neisseria meningitidis

There is no evidence that patients with solid organ transplants are at increased risk for CNS infections from Neisseria species. Indeed, it has recently been shown that it is safe to transplant organs procured from donors who died of bacterial meningitis due to N. meningitidis.

ATYPICAL BACTERIA

Nocardia asteroides

N. asteroides is an increasingly important opportunistic pathogen in immunosuppressed patients, particularly transplant recipients. Dissemination to other organs, especially the CNS and skin, occurs in up to 40% of transplant recipients with Nocardia infection. A presumptive diagnosis can be made by the direct visualization of filamentous, gram-positive, beaded rods that are partially acid fast in clinical specimens. The organism grows slowly in culture. Therefore, samples should be held for at least 3 weeks when Nocardia is suspected. Sulfonamides are considered standard therapy, although there is little evidence or data from comparative trials to support this. The clinical course is similar to that seen in patients without transplants.

Mycobacterium tuberculosis

Tuberculosis is a major source of morbidity and mortality in solid organ transplant recipients worldwide. In the United States, M. tuberculosis infection has been reported infrequently after renal transplantation (1%–4%) but is 20 times more frequent in this group than in the national population. Important risk factors for M. tuberculosis infection following transplantation include long duration of hemodialysis before transplantation, a history of tuberculosis, poor socioeconomic status, high-dose corticosteroid therapy for acute rejection, and residence in areas with a high prevalence of M. tuberculosis infection.

Clinical presentation and diagnosis. Patients with solid organ transplants have a higher rate of extrapulmonary and disseminated mycobacterial disease. M. tuberculosis infection of the CNS is an uncommon disease manifestation, but when it occurs, 3 main forms have been described: cerebral tuberculoma, meningitis, and myelopathy. M. tuberculosis is not the only species of mycobacteria that causes disease in patients with solid organ transplants. Transplant recipients also are susceptible to infections with M. avium and M. chelonae as well as other non-tuberculous mycobacteria. Acid-fast stains of the CSF should be obtained, and any biopsy specimens should be sent for mycobacterial culture. Since M. tuberculosis grows slowly, the specimens should be held for 6 weeks. Unfortunately, the sensitivity of the PCR assay for CNS tuberculosis is limited (approximately 80%).

Treatment and prognosis. A decision to treat for tuberculous meningitis should not depend entirely on
a PCR result, and therapy with a minimum of 3 drugs with CSF penetration should be initiated as soon as the disease is suspected. The outcome in cases of mycobacterial CNS infection is poor, with an estimated mortality of 14%.37

PARASITES
Toxoplasma gondii

Cats are the definitive hosts of T. gondii; they excrete infectious oocysts in their feces. Humans generally become infected by ingesting contaminated soil, food, or undercooked meat but can also acquire infection via maternal-fetal transmission, blood transfusion, or organ transplantation. In the United States, 10% to 40% of people are seropositive for Toxoplasma antibodies, which is considered evidence of latent infection.38 Reactivation of latent infection is responsible for most opportunistic CNS infections caused by T. gondii. In transplant recipients, toxoplasmosis may occur as the result of primary infection (ie, transplantation of an infected donor organ into a seronegative recipient) or reactivation of latent infection.

Clinical manifestations and diagnosis. Clinical manifestations of CNS toxoplasmosis in transplant recipients may include headache, altered mental status, seizures, focal neurologic deficits, hemiparesis, ataxia, and cranial neuropathy.6 Primary toxoplasmosis in the heart transplant recipient generally presents as myocarditis or cardiomyopathy. Rarely, the disease disseminates and may present as encephalitis or chorioretinitis in this setting.39 Definitive diagnosis requires identification of tachyzoites in biopsy samples, but identification of anti-T. gondii antibodies by enzyme-linked immunosorbent assay (ELISA) is a sensitive and specific method for determining exposure. PCR assay of CSF is highly specific and sensitive in some laboratories, but its sensitivity has been shown to be variable by laboratory and technique. Therefore, PCR assay should not be used to exclude the diagnosis of toxoplasmosis.40

Treatment. Solid organ transplant recipients with suspected CNS toxoplasmosis should receive pyrimethamine, folic acid, and sulfadiazine. For patients who report a sulfa allergy, sulfa desensitization or alternatives to sulfadiazine (eg, atovaquone, clarithromycin, azithromycin) should be considered.

Fungi
Aspergillus

Aspergillus is a common cause of CNS infection in the transplant recipient. CNS aspergillosis generally occurs during periods of more intense immunosuppression (eg, during treatment of rejection). CNS disease is generally accompanied other markers of disseminated disease, including evidence of pulmonary and/or gastrointestinal involvement.41

Clinical presentation and diagnosis. CNS aspergillosis is often rapidly progressive. It typically presents as altered mental status. Up to 41% of patients have seizures, and a focal neurologic defect is seen in approximately 30% of patients.42 The most common location for brain abscess is the frontoparietal region of the cerebral hemispheres, but the cerebellum or brainstem also may be involved. Diagnosis is made by identifying branching septate hyphae in patient specimens (sputum, CSF, biopsy material) or by positive culture in brain biopsy specimens, CSF, or pulmonary secretions. Aspergillus also has characteristic features on imaging. Chest CT may reveal the classic crescent or halo sign, and brain CT may show diffuse meningeal enhancement or multiple nonenhancing hypodense lesions in the basal ganglia or at the junction of the gray and white matter. Aspergillus is an angioinvasive fungus; thus, infarcts or hemorrhagic CNS lesions may also be observed.42

Treatment. Most experts recommend a combination of voriconazole and caspofungin for treatment of CNS aspergillosis.43 Although caspofungin’s penetration into the CSF is poor, there are anecdotal reports of enhanced success in treating CNS aspergillosis when this agent is combined with voriconazole.44,45

Candida

Candida may cause CNS disease in the setting of disseminated invasive candidiasis, manifesting as either meningitis or candidal CNS abscess. Imaging is often normal unless abscess is detected. Diagnosis is made by demonstration of the pathogen in CNS tissue or CSF.11 Treatment is with antifungal agents with good CSF penetration (eg, fluconazole).

Cryptococcus neoformans

C. neoformans has a propensity to cause CNS disease in patients with solid organ transplants.

Clinical presentation and diagnosis. C. neoformans causes meningitis in 98% of patients with CNS infection. Cryptococcoma presenting as a focal lesion is an unusual manifestation of CNS infection.46 Most cases of C. neoformans infection occur 6 months or more after transplantation. In a recent series of patients with CNS cryptococcosis, 62% had headache, 74% were febrile, and 48% had confusion or lethargy.46 Imaging may be normal or may reveal meningeal enhancement or an enhancing lesion. Diagnosis is made by detection of C. neoformans or CrAg in the CSF.

Treatment. Transplant patients require treatment
only for active infection.\textsuperscript{6} Treatment is with intravenous (IV) amphotericin B and flucytosine until the CSF is culture negative, at which point oral fluconazole may replace the IV antifungal agents. Fluconazole should be continued while the patient is maximally immunosuppressed. Lumbar puncture with culture and CrAg testing should be repeated after IV therapy is stopped and oral therapy is started and then repeated again every 2 to 4 weeks or if clinical deterioration occurs. If the CSF CrAg titer rises above the titer at initial diagnosis, treatment with amphotericin B and flucytosine should be repeated. Prophylactic treatment is required for 2 to 6 weeks after clearance of CrAg.

**Endemic Fungi**

As noted, the endemic fungi (ie, *H. capsulatum*, *B. dermatitidis*, *C. immitis*) usually cause CNS infection in the setting of systemic dissemination.  

**CNS histoplasmosis.** Manifestations of CNS histoplasmosis include meningitis, focal CNS lesions, cerebrovascular accidents caused by vascular involvement or cerebral emboli, and diffuse encephalitis.\textsuperscript{47} Prolonged fever is the predominant clinical finding in disseminated histoplasmosis. Patients may also present with subtle neurocognitive decline and, occasionally, focal neurologic findings. Chronic headache and seizures also may occur.\textsuperscript{47–49} In patients with meningitis, CSF abnormalities include lymphocytic pleocytosis, elevated protein, and hypoglycorrachia. CT or MRI may reveal single or multiple enhancing lesions in the brain or spinal cord of patients with parenchymal CNS involvement.\textsuperscript{47} Fungal stains of CNS tissues and urine testing for *H. capsulatum* antigen are used to diagnose CNS histoplasmosis. The course of *H. capsulatum* infections of the CNS is progressive and uniformly fatal if not treated. However, symptoms may at times be quite long-standing, and the speed of clinical deterioration is variable.\textsuperscript{47} Approximately 20% to 40% of patients with meningitis succumb to the infection despite optimal treatment.

**CNS blastomycosis.** The nervous system is involved in 5% to 10% of cases of disseminated blastomycosis. Epidural or cranial abscesses are the most commonly appreciated manifestations of CNS involvement with blastomycosis. Meningitis is a less common manifestation. It is not clear that blastomycosis is more common in patients with solid organ transplants. CNS infection by *B. dermatitidis* is notoriously difficult to diagnose. CT may direct biopsy of a cranial abscess, but identification of blastomycosis as the cause of meningitis is more problematic. Evaluation of CSF alone is rarely diagnostic. Ventricular fluid may be necessary to obtain a positive culture. In one series of 22 patients with CNS blastomycosis, CSF samples provided the diagnosis in only 2 patients, whereas ventricular fluid specimens were positive in 6 of 7 cases.\textsuperscript{40}

**CNS coccidioidomycosis.** Symptomatic coccidioidomycosis is more common in patients with abnormal cell-mediated immune function, such as solid organ transplant recipients.\textsuperscript{44} *C. immitis* infection of the CNS is the most deadly form of coccidioidomycosis. It most commonly presents as chronic granulomatous meningitis involving the basilar meninges. *C. immitis* may also produce focal CNS abscesses. The most common symptoms of CNS coccidioidomycosis are headache, nausea, vomiting, and altered neurocognitive status. Other symptoms and signs that may be observed include nuchal rigidity, diplopia, and other cranial neuropathies.\textsuperscript{51} The onset of symptoms is usually subacute to chronic. Initial CSF findings show a mononuclear pleocytosis, with low glucose and elevated protein concentrations. As many as 70% of patients have eosinophilic meningitis.\textsuperscript{51} A definitive diagnosis may be established by isolating the organism from a clinical specimen (eg, CSF, CNS tissue). *C. immitis* grows quickly in culture and can be seen as early as 2 days after inoculation. It is important to notify the clinical laboratory if *C. immitis* infection is suspected to minimize the risk of accidental exposure of laboratory personnel to infection.

**Treatment.** The optimal treatment for meningitis due to the endemic fungi is unknown, but an aggressive approach is recommended because of the poor outcome with some infections, such as histoplasmosis.\textsuperscript{48} Treatment with amphotericin B products over 3 to 4 months has been used most often. High-dose oral fluconazole is often continued for another 9 to 12 months after completion of amphotericin B therapy to reduce the risk for relapse. Liposomal amphotericin B might be considered for patients who have failed therapy with amphotericin B, followed by fluconazole. Chronic fluconazole maintenance therapy should be considered for patients who relapse despite full courses of therapy.\textsuperscript{48} Itraconazole is more active than fluconazole against *H. capsulatum*, but because it does not enter the CSF it is not used for treatment of meningitis. The Infectious Diseases Society of America (www.idsociety.org) publishes guidelines for the treatment of the endemic fungi.

**VIRUSES**

**Herpesviruses**

The human herpesviruses include HSV-1 and HSV-2, CMV, EBV, VZV, HHV-6, and HHV-8. All of these viruses are known to persist in the host after initial infection. Herpesviruses are the most frequent causes of infections in solid organ transplant recipients.
can occur as the result of primary infection or reactivation of latent infection. 

**HSV.** HSV is an important cause of CNS infections and accounts for 2% to 19% of cases of human encephalitis. In transplant recipients, prophylactic antiviral medication is typically prescribed, so HSV infection is uncommon. When HSV encephalitis occurs in such a patient, the clinician should be concerned about acyclovir-resistant HSV.

**EBV.** EBV infection can occur as a primary infection or reactivation of latent infection in solid organ transplant recipients. EBV has been associated with a number of neurologic syndromes, including meningoencephalitis, encephalitis, aseptic meningitis, Guillain-Barré syndrome, and Bell’s palsy. In solid organ transplant recipients, EBV infection and replication may also be associated with an abnormal proliferation of lymphoid cells. This condition is known as post-transplant lymphoproliferative disease (PTLD). The incidence of PTLD is highest during the first year after transplantation and most often occurs in patients who were EBV-seropositive before transplantation. In a series of 500 patients, PTLD involving the brain was seen in 2% of liver allograft recipients, 3% of heart transplant recipients, and 7% of heart-lung recipients. This variation is thought to be the result of differences in immune suppression. Patients with CNS involvement from PTLD generally present with mental status changes or a focal neurologic deficit. Diagnosis of PTLD is confirmed by demonstration of abnormal lymphoid proliferation in biopsy material. Quantitative PCR assay of the serum for EBV DNA correlates with increased risk of developing PTLD.

**CMV.** CMV is an uncommon cause of encephalitis or Guillain-Barré syndrome in solid organ transplant recipients. As noted, however, CMV is important as an immunomodulator and agent precipitating graft rejection.

**VZV.** In addition to causing chickenpox and shingles, VZV can produce a variety of CNS manifestations, including post-varicella cerebellitis, meningoencephalitis, vasculopathy, and acute aseptic meningitis. Primary infection with VZV can rapidly disseminate to multiple organs, including the CNS, in patients receiving immunosuppression after organ transplantation. Patients typically present with disseminated or CNS infection within 7 months after transplantation.

**HHV-6.** HHV-6 infection has been associated with encephalitis in solid organ transplant recipients. It is thought that reactivation of latent infection is responsible for most cases of infection, but transmission of virus from donor tissue can also occur.

### Other Viruses

**JC virus.** PML is a subacute progressive demyelinating disease of the CNS that can occur in transplant recipients. The clinical presentation in transplant patients is similar to that in patients with AIDS. Unlike other viral CNS infections, PML usually presents many months or years after transplantation. In more than 90% of patients with PML, reactivated latent JC virus infection can be detected by PCR assay of the CSF.

**Lymphocytic choriomeningitis (LCM) virus.** LCM virus is a rodent-borne arenavirus that can cause aseptic meningitis, encephalitis, or meningoencephalitis. In May 2005, the U.S. Centers for Disease Control and Prevention (CDC) received a report of severe illness in 4 patients who had received solid organ transplants from a common donor. All 4 patients subsequently were found to have evidence of infection with LCM virus. Preliminary findings from the ensuing investigation indicated that the source of infection likely was an infected hamster in the donor’s home. Three of the 4 organ recipients died within 27 days after transplantation. Based on the diagnosis of LCM, the surviving kidney transplant recipient was treated with intravenous ribavirin and reduction in his immunosuppressive drug regimen; the patient improved clinically. A similar case was reported in 2003, which involved the death of 3 patients who received organs infected by LCM virus. The CDC advises that health care providers should be aware that LCM virus can be transmitted through organ transplantation.

**West Nile virus.** West Nile virus continues to spread through North America. In immunocompetent patients, the majority of infections are asymptomatic. Early in this epidemic, it was observed that patients with solid organ transplants had unusually severe symptomatic community-acquired West Nile virus infection and were at greater risk for severe neurologic disease compared with the general population. In one small series reported in Canada (4 patients), the presenting symptoms included fever, confusion, headache, and weakness. The CSF showed a pleocytosis in all patients. Two patients had a full recovery, 1 had lower limb paralysis, and 1 died. Elevated CSF IgM is the test of choice for diagnosis of West Nile virus infection. Prevention of virus transmission and patient education about the mode of acquisition and mosquito bite prevention strategies may be more important in the transplant population than in the general population.

**Rabies virus.** Rabies is an acute, fatal encephalitis caused by neurotropic viruses in the genus *Lyssavirus*, family *Rhabdoviridae*. Most cases of rabies are caused by bites by rabid mammals. However, the CDC has
confirmed that rabies was the cause of death in 4 transplant recipients in whom encephalitis developed 3 to 4 weeks after transplantation. The common donor of all the transplanted organs had died of extensive subarachnoid hemorrhage of unknown etiology. According to eligibility screening and testing, the donor had had no contraindications to transplantation, although later a public health investigation revealed that the donor had reported being bitten by a bat. Infection with rabies virus likely occurred via neuronal tissue contained in the transplanted organs, as rabies virus is not spread hematologically.

CASE EXAMPLES

CASE 1

Presentation and Diagnostic Evaluation

A 53-year-old man presents to the emergency department for evaluation of the acute onset of a severe headache. The patient reports that he was doing well, in his usual state of health, until he recently traveled to Mexico to visit family. Shortly after his return, he noted some diarrhea followed by generalized body aches and then the acute onset of a severe headache. His medical history is significant for renal transplantation 3 years previously for obstructive uropathy.

A lumbar puncture is performed. CSF analysis shows a glucose level of 61 mg/dL, a protein level of 279 mg/dL, and a nucleated cell count of 1390/mm³. The differential on the cell count shows 72% neutrophils, 4% lymphocytes, and 24% monocytes. The patient is started on empiric therapy with ceftriaxone, ampicillin, vancomycin, and acyclovir. His antibiotic regimen is reduced to ampicillin only when the CSF culture grows out Listeria. The patient improves rapidly. Treatment with high-dose ampicillin is continued for 6 weeks.

Discussion

This renal transplant recipient is presenting in the late post-transplantation period with acute meningitis. The most common cause of acute bacterial meningitis in the solid organ transplant recipient is Listeria. The patient also noted diarrhea prior to the onset of meningitis, which is commonly seen in Listeria infection. Like many transplant recipients, this patient’s use of prophylactic TMP-SMX would have been discontinued 1 year after his renal transplantation. Use of this drug would have decreased the likelihood of acquiring meningitis from Listeria. Transplant recipients with Listeria meningitis require prolonged antibiotic coverage because of the risk of relapse with shorter courses (< 3 weeks) of therapy.

CASE 2

Presentation and Diagnostic Evaluation

A 39-year-old woman undergoes orthotopic heart transplantation secondary to giant cell myocarditis with no significant postsurgical complications. At home 3 months after transplantation, the patient notes a low-grade fever and headache over a period of several weeks. At this time, she undergoes a routine myocardial biopsy to monitor for rejection. During this visit, her neurologic examination reveals right gaze preference and left hand clumsiness. MRI of the brain shows a solitary lesion (Figure 2) that enhances with IV gadolinium. The heart biopsy shows filamentous structures in the endocardium and myocardium, consistent with Apergillus.

The patient is admitted to the hospital for further work-up for disseminated fungal infection, which reveals extensive disease in her lungs, brain, and both
eyes. She is started on caspofungin and voriconazole and responds well. One year after treatment, she remains disease free.

Discussion
This patient was in the intermediate post-transplantation period when she demonstrated a solitary brain lesion. It is in this period when most classic opportunistic pathogens are seen. Like many post-transplantation patients, this patient had evidence of fungal infection elsewhere in her body at the time of diagnosis. Diagnosis of the brain lesion was made by biopsy of her heart. Aspergillus is the most common cause of brain abscess in solid organ transplant recipients. CNS aspergillosis was previously associated with nearly 100% mortality. Use of the new antifungal agents, particularly voriconazole (because of its enhanced CNS penetration), has been associated with improved outcomes in CNS aspergillosis.

REFERENCES


