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Complications of Immunosuppressive/Immunomodulatory Therapy in Neurological Diseases

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Opinion statement

The first critical step in the appropriate treatment of neurological infectious disease accompanying immunosuppressive states or immunomodulatory medication is to properly identify the offending organism. Broadly immunosuppressive conditions will predispose to both common and uncommon infectious diseases. There are substantial differences between neurological infectious disorders complicating disturbances of the innate immunity (neutrophils, monocytes and macrophages) and those due to abnormal adaptive immunity (humoral and cellular immunity). Similarly, there are differences in the types of infections with impaired humoral immunity compared to disturbed cellular immunity and between T- and B-cell disorders. HIV/AIDS has been a model of acquired immunosuppression and the nature of opportunistic infections with which it has been associated has been well characterized and generally correlates well with the degree of CD4 lymphopenia. Increasingly, immunotherapies target specific components of the immune system, such as an adhesion molecule or its ligand or surface receptors on a special class of cells. These targeted perturbations of the immune system increase the risk of particular infectious diseases. For instance, natalizumab, an $\alpha 4\beta 1$ integrin inhibitor that is highly effective in multiple sclerosis, increases the risk of progressive multifocal leukoencephalopathy for reasons that still remain unclear. It is likely that other therapies that result in a disruption of a specific component of the immune system will be associated with other unique opportunistic infections. The risk of multiple simultaneous neurological infections in the immunosuppressed host must always be considered, particularly with a failure to respond to a therapeutic regimen. With respect to appropriate and effective therapy, diagnostic accuracy assumes primacy, but occasionally broad spectrum therapy is necessitated. For a number of opportunistic infectious disorders, particularly some viral and fungal diseases, antimicrobial therapy remains inadequate.

Keywords

Herpes simplex virus; Varicella zoster virus; JC virus; Progressive multifocal leukoencephalopathy; Fungal infections; Meningitis; Brain abscess; Listeria; Acyclovir;

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Valacyclovir; Famciclovir; Ganciclovir; Vancomycin; Ampicillin; Amphotericin B; Voriconazole; Fluconazole

Introduction

Immunosuppressives are employed in several contexts. Firstly, cancer currently affects more than 1.5 million people in the United States alone and chemotherapy that often broadly suppress immune function remains a mainstay of many therapeutic regimens. Autoimmune disorders are another class of diseases for which these therapies are used. In recent years, immunosuppressive regimens designed to abrogate immune-mediated tissue injury from various autoimmune diseases and graft versus host disease in organ transplants has been increasingly refined. Many of these treatments have been tailored to affect specific arms of the immune system. These targeted forms of immunosuppression have been referred to as immunomodulatory therapies. As with immunosuppressive regimens, many of these immunomodulatory medications, such as, natalizumab (α4β1 and α4β7integrin inhibitor), rituximab (anti-CD20), and alemtuzumab (anti-CD52), may also have the unintended consequence of the development of opportunistic infections; other immunomodulatory agents, such as, interferon-βs and glatiramer acetate, do not appear to carry this risk.

The brain seems to be particularly vulnerable due to the lack of adequate defense mechanisms and its relative isolation from the adaptive immune responses by the blood brain barrier. Since the brain is encased in a rigid bony structure, any swelling can lead to destruction of surrounding tissue. Treatment of these infections poses multiple challenges. Antimicrobial agents do not readily cross the blood brain barrier, thus, achieving adequate concentrations of these drugs can be difficult. Interference blood flow by damage to the cerebral vasculature by brain swelling and tissue necrosis in the infected tissues may also negatively impact the central nervous system (CNS) penetration of the antimicrobial agents. Infectious diseases resulting in brain abscess may require surgical intervention for adequate treatment. For some infections, such as, those caused by JC virus, no effective antiviral drug is available, and the most effective therapy has been efforts to restore immune function. However, a robust return of immune function, as may be observed with the removal of natalizumab, an α4β1 integrin inhibitor used in the treatment of multiple sclerosis or following the introduction of antiretroviral medications in the AIDS patient, may be associated with an exaggerated immune response to the offending microorganism, often with pernicious effects. This phenomenon has been termed the immune reconstitution inflammatory syndrome (IRIS). Treatment of neurological infections in the immunocompromised host is challenging. As has been repeatedly observed, often with latent infections readily controlled in the immunologically healthy host, such as, herpes virus and Cryptococcus, otherwise effective treatments may be insufficient to eradicate infections in the absence of some degree of immune response directed against the offending infection.

The neurological infectious disorders that complicate immunodeficiency states and immunosuppressive therapies are highly dependent on the nature and degree of immune system perturbation. Broadly immunosuppressive states and drugs will predispose to both common and unusual infections; whereas, abnormalities of a specific arm of the immune system increase the risk of specific diseases. Neutropenia or dysfunction predominantly

increases the risk of Gram-negative bacteria, staphylococcal infection, and certain fungal infections (*Candida*, *Aspergillus*, and mucormycosis). B cell disorders increase the risk of encapsulated bacterial infections and T lymphocyte dysfunction increases the risks of progressive multifocal leukoencephalopathy (PML), herpes infections, toxoplasmosis, *Cryptococcus*, and mycobacterial infection (Table 1.)

Treatment

Viral infections

Progressive multifocal leukoencephalopathy

- *Therapies implicated*: PML is caused by a ubiquitous polyomavirus, the JC virus. Immunomodulatory therapies associated with an increased risk of PML include natalizumab, rituximab, and efalizumab [1•]. Mycophenolate mofetil also carries a black box warning for PML. Any broadly immunosuppressive therapy may be associated with PML, but separating the contribution of the immune abnormality of the underlying disease from the therapy may be difficult.
- *Treatment*: The only unequivocal improvement in outcome attends restoration of immune function. Therefore, removing the offending agent is critically important and the aim of therapy is to restore immune function [2].

Withdrawal of immunomodulatory therapy: Discontinuation of the drug may be sufficient for drugs with a short half-life.

Removal of the drug by plasmapheresis (PLEX) may be needed. To date, PLEX has only been demonstrated to effectively remove natalizumab, and the effects on the immune system of some monoclonal antibody therapies, such as, rituximab, do not lend themselves to rapid reversal. Serum natalizumab concentrations are reduced by a mean of 92 % from baseline to 1 week after three PLEX sessions ($P<0.001$). Although average alpha4-integrin saturation was not reduced after PLEX because it was tightly bound to the lymphocytes, it was reduced to less than 50 % when natalizumab concentrations were below 1 μg/mL. Peripheral blood mononuclear cell (PBMC) transmigratory capacity increased 2.2-fold after PLEX ($P<0.006$), suggesting partial functional recovery [3].

Immune restoration is the cornerstone of treatment of PML; however, the inflammatory response associated with it may result in IRIS. This has been observed in the majority of patients treated for natalizumab associated PML and may be fatal [4, 5•, Class III] Early treatment with high-dose steroids (1 g/d of methyl prednisone for 5 days) is necessary followed by a slow oral taper over 2 months, as evidenced by analysis of retrospective studies [6, 7, Class IV].

Antiviral: Although several agents have been demonstrated to suppress JC virus replication in vivo, such as cytosine arabinoside [8], camptothecin [9], mefloquine [10], and, in some but not all studies, cidofovir [8, 11]. A carefully designed clinical trial of cytosine arabinoside for HIV-associated PML showed no benefit [12, Class I]. Observational trials

have failed to show any benefit of cidofovir in HIV-associated PML [13, 14, Class III]. Similarly, a trial of mefloquine that used cerebrospinal fluid (CSF) JC virus copy numbers as its primary endpoint failed to show an effect of the drug.

Human herpes virus-6 (HHV-6) encephalitis

- *Therapies implicated*: Organ transplants, allogenic stem cell transplants, particularly cord blood [15].
- *Treatment*: Reduction or elimination of immunosuppression is an important component of any treatment strategy of HHV-6 infection [16]. No randomized clinical trials have been conducted on antiviral drugs for the treatment of HHV-6 infection. Thus, there is no US Food and Drug Administration (FDA)-approved antiviral drug for HHV-6 infection. Nonetheless, ganciclovir, cidofovir, and foscarnet, either individually or in combination, have been used for the treatment of HHV-6–associated diseases. The efficacy of these drugs is based mainly on in vitro experimental data and on case reports.

Ganciclovir

Mechanism of action	Ganciclovir inhibits viral DNA polymerase, and thus prevents viral replication. To exert its antiviral properties, ganciclovir undergoes tri-phosphorylation into the active metabolite, ganciclovir triphosphate. The initial phosphorylation requires the enzyme phosphotransferase, which is expressed by HHV-6.
Standard dosage	5 mg/kg intravenously (IV) every 12 h for 14 to 21 days, followed by 5 mg/kg IV daily. The chronic maintenance dosage is 5 mg/kg/day IV 5 to 7 times weekly and should be continued until immune recovery has taken place and the virus can no longer be detected in the CSF.
Contraindications	Hypersensitivity to ganciclovir or acyclovir.
Main drug interactions	Generalized seizures may occur with imipenem/cilastatin. The concentrations of drugs excreted renally may increase as ganciclovir may be nephrotoxic. Probenecid can significantly decrease renal clearance of ganciclovir. Foscarnet, piperacillin, or total parenteral nutrition cannot be co-administered with ganciclovir intravenously since they may form a precipitate.
Main side effects	Renal toxicity is a major concern and close monitoring of renal function is required. Hematological toxicity is common with anemia being most frequent followed by leucopenia; rarely pancytopenia and thrombocytopenia can also occur. Hepatotoxicity can occur in 20 % of patients.
Special points	Some cases of HHV-6 infections may not respond to ganciclovir resulting in fulminant manifestations [17]. This could be due to the differential susceptibilities to ganciclovir between variants HHV-6A and HHV-6B with HHV-6B being less susceptible to ganciclovir when compared to HHV-6A [18]. Furthermore, mutations in the U38 DNA polymerase or the U69 phospho-transferase genes can lead to resistance to ganciclovir.

Foscarnet

Mechanism of action	It is a pyrophosphate analogue that inhibits viral replication by targeting viral DNA polymerase.
Standard dosage	Induction therapy is 90 mg/kg IV over 2 h every 12 h for 2 to 3 weeks; maintenance therapy is 90 to 120 mg/kg IV over 2 h, every 24 h.
Contraindications	Hypersensitivity to foscarnet.
Main drug interactions	Increased cardiac toxicity is seen with a large number of drugs including tricyclic antidepressants, halothane, fluconazole, pentamidine. and antipsychotics. Concurrent use of cidofovir can cause nephrotoxicity.
Main side effects	Anemia (33 %), granulocytopenic disorder (17 %), nausea, vomiting, and diarrhea (30 %).
Special points	It is often used in conjunction with ganciclovir or cidofovir. Drug resistance can emerge.

Cidofovir

Mechanism of action	Cidofovir is an acyclic nucleoside phosphonate analogue that has been shown to have excellent activity against HHV-6 in vitro.
Standard dosage	Induction therapy is 5 mg/kg via IV infusion given over 1 h once a week for 2 consecutive weeks; give saline hydration and probenecid (2 g orally 3 h before dose and 1 g orally at 2 h and 8 h after dose; total 4 g) before and after each infusion. Maintenance therapy is 5 mg/kg via IV infusion given over 1 h every other week with saline hydration and probenecid.
Contraindications	Hypersensitivity to cidofovir, probenecid, or sulfa-containing medications, serum creatinine greater than 1.5 mg/dL, creatinine clearance <55 mL/min, or a urine protein of 9100 mg/dL (equivalent to 92+ proteinuria), concomitant nephrotoxic agents.
Main drug interactions	Nephrotoxicity may affect any renally excreted drugs.
Main side effects	Nephrotoxicity (88 %), anemia (24 %), neutropenia (43 %), fever (58 %), alopecia (27 %), and rash (30 %).
Special points	It is considered second-line therapy against HHV-6 due to nephrotoxicity. A mutation in the U38 gene encoding DNA polymerase can cause resistance to cidofovir

Cytomegalovirus infection of the central nervous system

- *Therapies implicated*: An increased incidence of cytomegalovirus (CMV) has not been reported to date with immunomodulatory agents, but is observed with any chemotherapeutic regimen that results in widespread immunological deficiencies. As CMV is a common opportunistic infection with HIV/AIDS and typically associated with profound depletion of CD4 lymphocytes (<50 cells/mm^3) [19]. A correlation with low CD4 cell counts has also been observed in HIV-seronegative individuals [20].
- *Treatment*: No controlled clinical trials have been conducted for treating CMV encephalitis. Treatment regimens have been extrapolated from approved dosages for treating systemic CMV infection. Retrospective studies support combination therapy over monotherapy for CMV encephalitis [21•]. Pharmacological treatment of CMV encephalitis is similar to that of HHV-6 encephalitis, as detailed above.

Drug-resistant CMV: Drug resistant CMV is more commonly associated with encephalitis [22, Class IV]. Cell-based therapy using stored donor lymphocytes with or without in vitro expansion has been shown to be effective in transplant patients [23, 24, Class IV].

Herpes simplex virus-1 (HSV-1) encephalitis

- *Therapies implicated*: Although there appears to be an increased risk of HSV encephalitis and meningitis in patients with HIV/AIDS [25], there are little data regarding its incidence in individuals with other forms of immunosuppression. There have been isolated cases reported with natalizumab and fingolimod, a sphingosine-1-phosphate modulator that blocks lymphocyte egress from the lymph nodes.
- *Treatment*: Recently, the national guidelines for treatment of viral encephalitis were established for the United Kingdom [26]. This consensus statement recommended that all patients undergo neuroimaging studies prior to CSF evaluation. The etiological diagnosis is best made by polymerase chain reaction for the viral genome. While they suggested that there was no role for a

brain biopsy in the initial assessment of patients with suspected HSV encephalitis; it may be useful in patients with suspected HSV encephalitis who are CSF polymerase chain reaction (PCR) negative and deteriorating despite acyclovir to confirm the diagnosis or to identify alternative disorders.

Acyclovir

Standard dosage	10 mg/kg IV (over 1 h) given every 8 h; maximum of 20 mg/kg every 8 h. Duration of treatment in the original randomized trials of acyclovir for HSV encephalitis was 10 days. However, clinical relapse after 10 days treatment is known to occur [27, Class IV]. As a consequence, most clinicians now use at least 14 to 21 days intravenous treatment in confirmed cases. Some advocate repeating a CSF examination at 14 to 21 days, and continuing treatment until the CSF is negative of virus by PCR [27, Class IV]. A prolonged duration of therapy may be more important in the immunosuppressed patients.
Contraindications	Hypersensitivity to acyclovir or valacyclovir.
Main drug interactions	Due to induction of liver enzymes, drugs processed through the liver such as valproate and phenytoin may decrease in concentration. Due to effects on the kidney, drugs excreted through the kidney may increase in concentration with concomitant use with acyclovir.
Major side effects	Nephrotoxicity, thrombotic thrombocytopenic purpura, Stevens Johnson syndrome (rare).
Special points	Oral valacyclovir has been used in pediatric practice, especially when maintaining intravenous access has proved difficult; in adults it may have a role in ongoing treatment, particularly in patients with HSV detectable in the CSF after 2 to 3 weeks. The NIAID Collaborative Antiviral Study Group is assessing the role of high-dose valacyclovir (2 g three times daily) for 3 months [28].

Corticosteroids: Corticosteroid use in HSVE remains controversial. A retrospective analysis of 45 patients with HSV encephalitis showed that older age, lower Glasgow Coma Score on admission, and lack of administration of corticosteroids were significant independent predictors of a poor outcome [29, Class III]. A randomized placebo-controlled trial is now under way [30].

Varicella zoster virus infection

- *Therapies implicated*: In immunosuppressed patients, single or multidermatomal eruptions of shingles may occur. Unusual presentations may include a CNS or retinal vasculitis with infarcts in the absence of a rash. Rarely, it may cause acute encephalitis without a vasculitis or a rash [31]. In the United States, three drugs have been approved for treatment: acyclovir, valacyclovir, and famciclovir. In Europe, brivudin is also approved for treatment. All CNS complications should be treated with IV acyclovir while shingles can be treated with oral valacyclovir or famciclovir.

Famciclovir

Standard dosage	Shingles: 500 mg orally every 8 h for 7–10 days. Dosage needs to be adjusted in patients with renal insufficiency.
Contraindications	Hypersensitivity to the drug.
Major drug interactions	None.
Major side effects	Headaches (10–40 %), dysmenorrhea (1–8 %), erythema multiforme (rare)
Special points	Famciclovir is a prodrug that gets metabolized to penciclovir which is the active form of the drug.

Primary CNS lymphoma associated with Epstein-Barr virus infection

- *Therapies implicated*: Primary CNS lymphoma (PCNSL) with associated Epstein-Barr virus (EBV) infection is observed with an increased frequency in HIV/AIDS and with immunosuppressive regimens. Rare case reports of PCNSL with and without EBV infection have been reported with natalizumab [32] and mycophenolate mofetil [33, 34]. However, the relative infrequency of these cases precludes meaningful comment about an association with these agents.
- The consensus treatment of AIDS-related PCNSL according to most national comprehensive cancer center network guidelines is the use of high-dose methotrexate-based chemotherapy with or without whole brain irradiation [35, Class IV]. Some consider a combination of methotrexate and cytarabine as the treatment standard [36, Class IV]. Rituximab alone or in combination with other therapies has also been suggested [37, 38], particularly, in relapsed or recurrent disease [39, Class IV]. There is no effective treatment for Epstein-Barr virus and there is no evidence that EBV-associated PCNSL should be treated any differently than PCNSL without EBV.

Bacterial infections

- *Treatment*: Almost any bacterial infection can occur in immune-suppressed patients, resulting in meningitis, meningoencephalitis, or brain abscesses. A laboratory diagnosis is essential to determine the etiological organism and its antimicrobial sensitivity. Patients with neutropenia are at particular risk for meningitis due to *Pseudomonas aeruginosa* and other enterobacteria. Because these patients are unable to mount an effective inflammatory response, they may have minimal meningeal symptoms despite serious infection. Patients with neutropenia and meningitis should be empirically treated with a third-generation cephalosporin (eg, ceftazidime to provide *Pseudomonas* coverage) and vancomycin, pending culture and sensitivity results. Guidelines for management of bacterial meningitis have been established by the European Federation of Neurological Societies [40, Class IV].

Listeria meningitis and brain abscess

- Immunosuppressed individuals are predisposed to the development of *Listeria* meningitis. They are typically exposed to the organism following ingestion of contaminated (usually unpasteurized) food. *Listeria* causes a rhombencephalitis or brain stem abscess.
- *Treatment*: The antibiotics vancomycin and ampicillin in combination is the treatment of choice. They have a synergistic effect against the organism and hence the combination treatment is necessary. However, in one retrospective study gentamicin was found to have no significant benefit in treatment of *Listeria* meningitis [41, Class II]. Patients who are allergic to penicillin can be treated with trimethoprim-sulfamethoxazole, meropenem, or moxifloxacin.

These alternative treatments are based on case reports or experimental studies [42, Class IV]. *Listeria* is intrinsically resistant to the cephalosporins.

Vancomycin

Standard dosage	60 mg/kg/24 h as continuous infusion (adjusted for creatinine clearance) after 15 mg/kg loading dose aiming for serum levels of 15–25 mg/L.
Contraindications	Hypersensitivity to vancomycin.
Main drug interactions	Histamine-like reaction with concomitant anesthetic agents. Monitor carefully with neurotoxic or nephrotoxic drugs.
Main side effects	Overgrowth of non-susceptible organisms, nephrotoxicity, skin necrosis with inadvertent extravasation, thrombophlebitis, and reversible neutropenia.
Cost	Moderately expensive.

Ampicillin

Standard dose	Ampicillin 2 g intravenously every 4 h.
Contraindications	Hypersensitivity to penicillins.
Main drug interactions	Avoid the concomitant administration of allopurinol.
Main side effects	Skin rash, urticaria, and gastrointestinal symptoms.
Cost:	Inexpensive.

Alternative treatments: Trimethoprim–sulfamethoxazole 10–20 mg/kg 6–12 hourly; meropenem 2 g/8 h or moxifloxacin 400 mg/day. Duration of treatment: 1 month, in some longer treatment may be needed. Patients should be monitored with repeated brain MRI and CSF evaluations.

Tuberculosis

- *Therapies implicated*: Immunosuppressive conditions, particularly, the use of corticosteroids, increase the risk of reactivation of tuberculosis. The immunomodulatory agents that affect tumor necrosis factor, including infliximab, adalimumab, and etanercept, appear to increase the risk of tuberculosis [43•].
- The optimal treatment regimen remains undefined and largely empirical. Isoniazid, pyrazinamide, and ethionamide penetrate readily into CSF, whereas, rifampin, ethambutol, and streptomycin do so poorly, especially in noninflamed meninges. Various regimens employing isoniazid and rifampicin with or without pyrazinamide, streptomycin, and ethambutol have been proposed. Treatment regimens vary with the probability of drug resistance (Tables 2 and 3). The World Health Organization guidelines recommend 6 months of therapy, but other guidelines recommend 9 to 12 months of anti-tuberculous therapy [44, Class IV].
- Concomitant corticosteroid therapy reduces mortality in tuberculous meningitis and has increased survival and decreased sequelae in children [45, 46, Class II]. However it appears to have had no effect on the frequency of increased intracranial pressure, hydrocephalus, or basal ganglia infarcts [46, Class II].

Isoniazid

Standard dosage	5 mg/kg up to 300 mg daily in a single dose.
Contraindications	Hypersensitivity to the drug including history of a previous isoniazid-associated hepatic injury.
Major side effects	Peripheral neuropathy, hepatic dysfunction, gastrointestinal symptoms, hematological disturbances, hypersensitivity reactions, and pyridoxine deficiency.
Major drug interactions	May interact with acetaminophen, carbamazepine, ketoconazole, phenytoin, theophylline, and valproate.
Special points	Category C drug in pregnancy.
Cost	Inexpensive.

Rifampicin

Standard dosage	10 mg/kg in a single dose not to exceed 600 mg/day.
Contraindications	Hypersensitivity to the drug including history of a previous isoniazid-associated hepatic injury.
Major side effects	Transient hepatic dysfunction, gastrointestinal symptoms, hematological disturbances, particularly, thrombocytopenia, and headache.
Major drug interactions	Avoid concomitant administration of saquinavir. May accelerate the metabolism of a wide variety of drugs by inducing cytochrome P-450 enzymes.
Special points	Should be administered either 1 h before or 2 h after a meal.
Cost	Inexpensive.

Streptomycin

Standard dosage	15 mg/kg in adults if administered daily and 25–30 mg/kg if administered twice or thrice weekly with a maximum dose of 1.5 g.
Contraindications	Hypersensitivity to the drug.
Major side effects	Vestibular ototoxicity, facial paresthesias, rash, fever, urticaria, angioneurotic edema, and eosinophilia.
Major drug interactions	Ototoxic effects accentuated with co-administration of ethacrynic acid, furosemide, mannitol and possibly other diuretics.
Special points	Category D drug in pregnancy.
Cost	Inexpensive.

Brain abscess

- *Common organisms*: Variety of gram-positive and negative bacteria, nocardia, fungi, particularly aspergillosis and mucormycosis.
- *Treatment*: Surgical drainage is the treatment of choice if diameter is greater than 2 cm in size.
- Antibacterial therapy depending on antibiotic sensitivity for treatment of CNS infection and any peripheral sites of infection.

Fungal infections

- *Therapies implicated*: Immunosuppressive regimens that result in neutropenia increase the risk of candidal infections. Neutrophil dysfunction, particularly, in the setting of hyperglycemia, increases the risk of mucormycosis. Therapies that alter cell-mediated immunity increase the risk of all fungal infections that grow as yeast forms in the CNS, such as, *Cryptococcus* and histoplasmosis.

Common observed fungal disorders include cryptococcal meningitis, *Candida* meningitis, aspergillosis.

Amphotericin B

Mechanism of action	It acts by binding to sterols in the fungus cell membrane, producing a change in membrane permeability that allows leakage of intracellular components from the cell.
Standard dosage	Cryptococcal meningitis: Amphotericin B: 0.7 to 1 mg/kg/day IV or lipid formulation amphotericin B 4–6 mg/kg IV daily plus flucytosine 100 mg/kg/day orally in 4 divided doses for 4 to 6 weeks (induction), followed by fluconazole 400 mg/day orally for 8 weeks (consolidation), then fluconazole 200 mg/day orally for 6 to 12 months (maintenance).
Major side effects	Hypotension, cardiac dysrhythmia, normochromic, normocytic anemia, agranulocytosis, nephrotoxicity, hypokalemia, thrombophlebitis. Dosages of 1.5 mg/kg/day can cause cardiac arrest.
Major drug interactions	Concomitant use of nephrotoxic medications or those with cardiac effects should be avoided or closely monitored.
Special points	It is the drug of choice for most CNS mycoses despite limited CNS penetration. Liposomal preparations have better penetration and lower toxicity. In select cases can be given intrathecally.

Voriconazole

Standard dosage	Aspergillosis: initial loading dose 6 mg/kg IV every 12 h for 2 doses, followed by 4 mg/kg IV every 12 h; may switch to oral dosing with 200 mg every 12 h as tolerated. May require treatment for 1 year. CNS candidiasis: may treat initially with amphotericin B followed by oral voriconazole as maintenance therapy.
Contraindications	Concomitant use of carbamazepine, CYP3A4 substrates (terfenadine, astemizole, cisapride, pimozide, or quinidine), ergot alkaloids, long-acting barbiturates, rifabutin, rifampin, sirolimus, or St. John's wort. Hypersensitivity to the drug.
Major side effects	Visual disturbance (21 %), hallucinations (2.4 % to 16.6 %), rash (7 %). Hepatitis, pancreatitis, toxic encephalopathy and prolonged QT interval are rare.
Major drug interactions	Drugs that induce liver enzymes can reduce plasma concentrations of voriconazole. Drugs with cardiac effects should be monitored closely. It may displace protein-bound drugs such as fosphenytoin to increase their concentration.
Special points	It is the drug of choice for aspergillosis.

Fluconazole

Mechanism of action	It is a triazole antifungal agent that inhibits fungal sterol synthesis leading to aggregation of 14 alpha-methyl sterols in the fungi, which are responsible for the fungistatic activity.
Standard dosage	Most often used as step-down therapy after initial treatment with amphotericin B. But can be used as initial therapy with 400–800 mg (6–12 mg/kg) IV or orally daily. Maintenance dosage is 200 mg/day for cryptococcal meningitis but 400–800 mg/day for other CNS fungal infections until resolution of clinical and laboratory parameters. Empirical antifungal therapy: loading dose 800 mg IV or orally, followed by 400 mg (6 mg/kg) IV or orally daily.
Major side effects	Prolonged QT interval and agranulocytosis are rare.
Major drug interactions	Similar to voriconazole.
Special points	It is a well tolerated drug that can be administered both by mouth and IV. It has good penetration into the CSF. Used as a second-line drug.

5-Fluorocytosine: Has excellent penetration to the CSF, but its use is limited due to its myelotoxicity. Blood level determinations can avoid this toxicity. Used in conjunction with other antifungals. If used alone can lead to drug resistant organisms.

Surgical intervention: CSF drainage and shunting if hydrocephalus is present, most often seen with cryptococcal meningitis; resection of mass or drainage of abscess is necessary in

most cases of aspergillosis. Resection of infected tissues is also critical in the treatment of mucormycosis.

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Table 1

Correlation of nature of underlying immunosuppression with likely infectious agent

Neutrophil deficits (absolute neutropenia or functional abnormalities)
Bacteria
Enteric Gram-negative bacteria
Staphylococcus
Fungi
Candida
Aspergillosi
Mucormycosis
Abnormal T cell or monocytes
Viruses
Herpes (CMV, HSV1 and 2, VZV)
JC virus (PML)
Parasites
Toxoplasmosis
Strongyloides stercoralis
Fungi (typically yeast forming)
Cryptococcus
Histoplasmosis
Blastomycosis
Bacteria
Mycobacteria
Nocardia
Listeria
Disorders of humoral immunity
Bacteria
Streptococcus pneumoniae
Neisseria meningitidis
Haemophilus influenzae

(*Adapted from* Berger [47])

Table 2

Treatment of tuberculous meningitis with low probability of drug resistance

Drug	Usual daily dose	Maximum dose	Duration
Isoniazid	5–10 mg/kg	300 mg	6 months
Rifampin	10–20 mg/kg	600 mg	6 months
Pyrazinamide	15–30 mg/kg	2,500 mg	2 months
		OR	
Isoniazid	5–10 mg/kg	300 mg	9 months
Rifampin	10–20 mg/kg	600 mg	9 months
Ethambutol	15–25 mg/kg		2 months
		OR	
Streptomycin	15 mg/kg	1,000 mg	2 months
Isoniazid	5–10 mg/kg or 15 mg/kg (2× week)	900 mg	8 months
Rifampin	10–20 mg/kg or 10–20 mg/kg (2× week)	600 mg	8 months

Table 3

Treatment of tuberculous meningitis with a high probability of drug resistance

Drug	Usual daily dose	Duration
Isoniazid	5–10 mg/kg	12months
Rifampin	25 mg/kg	12months
Pyrazinamide	15–30 mg/kg	2 months
Ethambutol or Streptomycin	25 mg/kg	2 months
	15 mg/kg	2 months