Herpes Simplex Virus

Linear esophageal ulcers caused by herpes simplex virus (HSV) and Candida. Infection with HSV-1 and -2 leads to stomatitis and esophagitis post-transplantation without acyclovir prophylaxis. Additionally, paronychia, corneal ulcers, encephalitis, genital lesions, disseminated involvement of the gastrointestinal tract, pancreas, and liver, and interstitial nephritis has been seen. HSV-6 causes exanthem subitum in children, mononucleosis, and hepatitis. There has been some evidence that reactivation infections may be associated with rejection in transplant recipients. Both reactivation and reinfection may occur. HSV-8 is associated with Kaposi’s sarcoma. Prevention of these infections has been achieved using prophylactic acyclovir following transplantation. If clinical symptoms occur from HSV, they usually are treated with acyclovir adjusted for renal function.

94% of adults have evidence of a prior VZV infection. In those patients previously infected, antibody titers increase following transplantation. Pretransplant screening is recommended to advise the patient on treatment of post-transplant exposures. Post-transplant exposures to zoster or chickenpox in the nonimmune individual should be treated with acyclovir, famcyclovir, or varicella-zoster immune globulin. Immune globulin is rarely required at this time. Patients with the new onset of varicella infection following transplantation or with diffuse zoster should be treated with intravenous acyclovir, 10 mg/kg, three times per day, or famcyclorir depending on renal function. Infection in the transplant recipient, particularly in those who are primarily infected, can result in encephalitis, disseminated intravascular coagulation, pneumonia, bowel involvement, pancreatitis, dermatitis, and hepatitis.

The attack rate in nonimmune individuals of household contacts with varicella infections is 80% to 90%. Therefore, if individuals have not previously had varicella infections at the time of transplant evaluation, vaccination with a live attenuated strain could be considered. Recently this strategy has been used in children prior to renal transplantation. Attack rates in vaccinated individuals may be up to 31%, but the disease that develops is much milder compared with those susceptible individuals not previously vaccinated. Should resistant strains of varicella develop, foscarnet has been effective. Foscarnet is associated with a renal decline in renal function.

(Adapted from Friedman-Kien [31]; with permission.)
Adenovirus has been shown to infect the bladder, uroepithelial cells, renal tubular cells (distal greater than proximal), the endothelium of the glomeruli and peritubular capillaries, and, occasionally, mesangial cells. The outcome of adenovirus infection is related to the type of immunosuppression and the recipient age. The death rate during active infection in renal transplantation may be as high as 18% but may be even higher in younger patients. The onset of disease after transplantation is usually within 6 months of the transplant.

Clinically, the most frequent symptoms of an adenovirus infection involve difficult micturition, including gross hematuria, fever, and, occasionally, renal dysfunction. The diagnosis is suspected when bacterial cultures are negative but there is gross hematuria. The urinary symptoms usually last 2 to 4 weeks. The diagnosis is made by urine culture or by electron microscopy or light microscopy, where adenoviruses are seen as intranuclear basophilic viral inclusions with a narrow halo between the inclusions and the nuclear membrane. Treatment has been somewhat successful using ganciclovir. Interferon therapy is difficult because of the risk of acute renal failure or rejection in transplant recipients. Furthermore, efficacy is questionable because of the virus’ ability to inhibit the mode of action of interferon. Ribavirin has successfully cleared the virus in several immunosuppressed patients. The use of IVIG has not been associated with reliable results. In the future, cidofovir may also be used for the treatment of adenovirus infections, but renal insufficiency and proteinuria may limit use.

### CENTRAL NERVOUS SYSTEM INFECTION IN THE TRANSPLANT RECIPIENT

**Incidence 5%; mortality up to 85% for CNS infections**

**Acute to subacute**
- L. monocytogenes

**Subacute to chronic**
- Cryptococcus neoformans
- Mycobacterium tuberculosis
- Coccioidiodes immitis

**Focal brain infection**
- Aspergillus
- L. monocytogenes
- T. gondii
- N. asteroides
- Candida albicans
- Cryptococcus

**Progressive dementia**
- Polymavirus, HSV, CMV, HIV

**Symptoms**
- Headache—may be mild, may have little meningismus
- Fever—may be mild
- ± altered consciousness
- Cerebrospinal fluid
- Lymphocytic pleocytosis
- (viral/fungal/MTB)
- Hypoglycorrhaha
- Neutrophilic pleocytosis (bacterial)

Over three-fourths of central nervous system infection is accounted for by
- L. monocytogenes
- C. neoformans
- A. fumigatus

**Timing**
- Early
  - Listeria
  - Nocardia
  - Toxoplasma
  - Aspergillus
- Late—as above and due to chronic enhanced immunosuppression plus Cryptococcus and tuberculosis

**Diagnosis**
- Physical examination
- CT scan identifies hypodense ring-enhancing lesions
- CSF examination
- Directed lesional aspirates
CAUSES OF HEADACHE IN THE TRANSPLANT RECIPIENT

Medications
- OKT3 (aseptic meningitis)
- ATG
- IVlgG
- Cyclosporine
- Tacrolimus
- Antihypertensives
  - Calcium channel blockers
  - ACE inhibitors
- Nitrates
- Hydralazine
- Minoxidil
- Hypertension
- Neck “tension,” muscle pulls, ligamental irritation
- Sinusitis
- Ocular abnormalities
- Excessive vomiting
- Migraine headaches exacerbated by cyclosporine, tacrolimus, and calcium channel blockers
- Stroke
- Infection of the central nervous system

FIGURE 10-57
Causes of headache in the transplant recipient. ACE—angiotensin-converting enzyme; CNS—central nervous system; ATG—antithymocyte globulin.

WORK-UP OF AN UNEXPLAINED HEADACHE

History
- Character, pattern, positional relationships
- Fever, duration of headache and fever
- Location of headache
- Visual, movement, sensory impairment
- Bowel or bladder incontinence
- Trauma
- Medications old and new
- Time of medications and relationships to headache

Physical examination
- Eye
- Neurological
- Complete the rest of the examination

If no papilledema or focal neurological deficit—lumbar puncture
If papilledema or focal deficit→CT first if no mass lesion→lumbar puncture

Cerebrospinal fluid is sent for
- Cell count and differential
- Protein
- Glucose
- Gram's stain
- Fungal stains
- Acid fast stain
- Fungal culture
- Mycobacterial cultures
- Bacterial cultures
- Cryptococcal antigen
- Save cerebrospinal fluid in addition for other tests including Histoplasma capsulatum or Coccidioides immitis antibody titers

FIGURE 10-58
Work-up of an unexplained headache.

FIGURE 10-59
Epstein-Barr virus (EBV). EBV is associated with asymptomatic infection, mononucleosis, hepatitis, and, rarely, interstitial nephritis. In transplant recipients, posttransplant lymphoproliferative disorder (PTLD) is also associated with EBV. EBV promotes B-cell proliferation, if left unchecked by immunosuppressive agents targeting the T-cell system. This chest radiograph shows multiple pulmonary nodules of PTLD. Symptoms vary from no symptoms to diffuse organ involvement causing dysfunction. Any area of the body may be involved, with frequent sites being the gums, chest, abdomen, and central nervous system.

PTLD occurs during the first posttransplant year in approximately 50% of those developing PTLD. It is seen in 1% to 2% of renal transplant recipients. Primary EBV infection following transplantation and antilymphocyte agent use is associated with an increased risk. Increasing quantitative blood EBV DNA levels may predict the onset of PTLD.