Acute interstitial nephritis caused by TMP-SMX is rare. However, because transient increases in creatinine (artifactual) and hyperkalemia (manageable) can occur, early discontinuation of prophylaxis, especially after kidney transplantation, is recommended by some groups. Although additional monitoring is indicated, the benefits of TMP-SMX in kidney transplant recipients may outweigh the risks; otherwise, second-line prophylactic agents should be used. *Nocardia* infection (Chap. 199) may present in the skin, bones, and lungs or in the CNS, where it usually takes the form of single or multiple brain abscesses. Nocardiosis generally occurs ≥1 month after transplantation and may follow immunosuppressive treatment for an episode of rejection. Pulmonary manifestations most commonly consist of localized disease with or without cavities, but the disease may be disseminated. The diagnosis is made by culture of the organism from sputum or from the involved nodule. As it is for *P. jirovecii* infection, prophylaxis with TMP-SMX is often efficacious in the prevention of nocardiosis.

Toxoplasmosis can occur in seropositive patients but is less common than in other transplantation settings, usually developing in the first few months after kidney transplantation. Again, TMP-SMX is helpful in prevention. In endemic areas, histoplasmosis, coccidioidomycosis, and blastomycosis may cause pulmonary infiltrates or disseminated disease.

Late Infections Late infections (>6 months after kidney transplantation) may involve the CNS and include CMV retinitis as well as other CNS manifestations of CMV disease. Patients (particularly those whose immunosuppression has been increased) are at risk for subacute meningitis due to *Cryptococcus neoformans*. Cryptococcal disease may present in an insidious manner (sometimes as a skin infection before the development of clear CNS findings). *Listeria* meningitis may have an acute presentation and requires prompt therapy to avoid a fatal outcome. TMP-SMX prophylaxis may reduce the frequency of *Listeria* infections.

Patients who continue to take glucocorticoids are predisposed to ongoing infection. "Transplant elbow," a recurrent bacterial infection in and around the elbow that is thought to result from a combination of poor tensile strength of the skin of steroid-treated patients and steroid-induced proximal myopathy, requires patients to push themselves up with their elbows to get out of chairs. Bouts of cellulitis (usually caused by *S. aureus*) recur until patients are provided with elbow protection.

Kidney transplant recipients are susceptible to invasive fungal infections, including those due to *Aspergillus* and *Rhizopus*, which may present as superficial lesions before dissemination. Mycobacterial infection (particularly that with *Mycobacterium marinum*) can be diagnosed by skin examination. Infection with *Prototheca wickerhamii* (an achlorophyllic alga) has been diagnosed by skin biopsy. Warts caused by human papillomaviruses (HPVs) are a late consequence of persistent immunosuppression; imiquimod or other forms of local therapy are usually satisfactory. Merkel cell carcinoma, a rare and aggressive neuroendocrine skin tumor whose frequency is increased fivefold in elderly SOT (especially kidney) recipients, is causally linked to a novel polyomavirus, Merkel cell polyomavirus.

Notably, although BK virus replication and virus-associated disease can be detected far earlier, polyomavirus-associated nephropathy is clinically diagnosed in a median of ~300 days and thus qualifies as a late-onset disease. With the establishment of better screening procedures (e.g., urine cytology, urine nucleic acid load, plasma PCR), disease onset is being detected earlier (see "Middle-Period Infections," above) and preemptive strategies (decrease or modification of immunosuppression) are being instituted more promptly, as the efficacy of antiviral therapy is not well established.

HEART TRANSPLANTATION

Early Infections Sternal wound infection and mediastinitis are early complications of heart transplantation. An indolent course is common, with fever or a mildly elevated white blood cell count preceding the development of site tenderness or drainage. Clinical suspicion based on evidence of sternal instability and failure to heal may lead to the diagnosis. Common microbial residents of the skin (e.g., *S. aureus*, including methicillin-resistant strains, and *Staphylococcus epidermidis*) as well as gram-negative organisms (e.g., *Pseudomonas aeruginosa*) and fungi (e.g., *Candida*) are often involved. In rare cases, mediastinitis in heart transplant recipients can also be due to *Mycoplasma hominis* (Chap. 212); since this organism requires an anaerobic environment for growth and may be difficult to see on conventional medium, the laboratory should be alerted that its involvement is suspected. *M. hominis* mediastinitis has been cured with a combination of surgical debridement (sometimes requiring muscle-flap placement) and the administration of clindamycin and tetracycline. Organisms associated with mediastinitis may sometimes be cultured from pericardial fluid.

Middle-Period Infections *T. gondii* (Chap. 253) residing in the heart of a seropositive donor may be transmitted to a seronegative recipient. Thus serologic screening for *T. gondii* infection is important before and in the months after cardiac transplantation. Rarely, active disease can be introduced at the time of transplantation. The overall incidence of toxoplasmosis is so high in the setting of heart transplantation that some prophylaxis is always warranted. Although alternatives are available, the most frequently used agent is TMP-SMX, which prevents infection with *Pneumocystis* as well as with *Nocardia* and several other bacterial pathogens. CMV also has been transmitted by heart transplantation. *Toxoplasma*, *Nocardia*, and *Aspergillus* can cause CNS infections. *L. monocytogenes* meningitis should be considered in heart transplant recipients with fever and headache.

CMV infection is associated with poor outcomes after heart transplantation. The virus is usually detected 1–2 months after transplantation, causes early signs and laboratory abnormalities (usually fever and atypical lymphocytosis or leukopenia and thrombocytopenia) at 2–3 months, and can produce severe disease (e.g., pneumonia) at 3–4 months. An interesting observation is that seropositive recipients usually develop viremia faster than patients whose primary CMV infection is a consequence of transplantation. Between 40% and 70% of patients develop symptomatic CMV disease in the form of (1) CMV pneumonia, the form most likely to be fatal; (2) CMV esophagitis and gastritis, sometimes accompanied by abdominal pain with or without ulcerations and bleeding; and (3) the CMV syndrome, consisting of CMV in the bloodstream along with fever, leukopenia, thrombocytopenia, and hepatic enzyme abnormalities. Ganciclovir is efficacious in the treatment of CMV infection; prophylaxis with ganciclovir or possibly with other antiviral agents, as described for renal transplantation, may reduce the overall incidence of CMV-related disease.

Late Infections EBV infection usually presents as a lymphoma-like proliferation of B cells late after heart transplantation, particularly in patients maintained on intense immunosuppressive therapy. A subset of heart and heart-lung transplant recipients may develop early fulminant EBV-LPD (within 2 months). Treatment includes the reduction of immunosuppression (if possible), the use of glucocorticoid and calcineurin inhibitor–sparing regimens, and the consideration of therapy with anti–B cell antibodies (rituximab and possibly others). Immunomodulatory and antiviral agents continue to be studied. Ganciclovir prophylaxis for CMV disease may indirectly reduce the risk of EBV-LPD through reduced spread of replicating EBV to naïve B cells. Aggressive chemotherapy is a last resort, as discussed earlier for HSC transplant recipients. KSHV-associated disease, including Kaposi's sarcoma and primary effusion lymphoma, has been reported in heart transplant recipients. GVHD prophylaxis with sirolimus may decrease the risk of both rejection and outgrowth of KSHV-infected cells. Antitumor therapy is discussed in Chap. 103e. Prophylaxis for *Pneumocystis* infection is required for these patients (see "Lung Transplantation, Late Infections," below).

LUNG TRANSPLANTATION

Early Infections It is not surprising that lung transplant recipients are predisposed to the development of pneumonia. The combination of ischemia and the resulting mucosal damage, together with accompanying denervation and lack of lymphatic drainage, probably contributes to the high rate of pneumonia (66% in one series). The