31 Infection in Kidney Transplant Recipients

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Overview

Successful management of infections in kidney transplant recipients is a function of the immune status of the host and the epidemiology of infectious exposures. Transplant recipients are susceptible to a broad spectrum of infectious pathogens while manifesting diminished signs and symptoms of invasive infection. Thus the diagnosis of infection is more difficult in transplant recipients than in immunologically normal individuals. The interactions between infection, immunosuppression, and immune function often result in clinical syndromes reflecting multiple simultaneous processes, such as infection and graft rejection. Immunocompromised patients tolerate invasive infection poorly, with high morbidity and mortality, lending urgency to the need for an early, specific diagnosis to guide antimicrobial therapy. Given the predominant T-lymphocyte dysfunction inherent to transplant immunosuppression, viral infections are a major contributor to morbidity resulting in graft dysfunction, graft rejection, systemic illness, and increased risk for other opportunistic infections (e.g., *Pneumocystis* and *Aspergillus*) and virally mediated cancers.

Risk of Infection

The risk of infection in a kidney transplant recipient is determined by the interaction of two key factors:

1. The epidemiologic exposures of the patient, including the timing, intensity, and virulence of the organisms encountered.
2. The patient's "net state of immunosuppression," a conceptual measure of all the factors that contribute to the host's risk of infection.[1,2]

The importance of any infectious exposure is determined by the ability of the host to deal effectively with the pathogen. Thus the immunosuppressed diabetic with vascular disease is at greater risk of bacterial skin infections than is a comparable immunosuppressed nondiabetic. Understanding the risk factors for each transplant recipient allows development of a differential diagnosis for infectious syndromes and development of preventive strategies (prophylaxis, vaccination) appropriate to the individual's unique risks.[3,4]

EPIDEMIOLOGIC EXPOSURES

Epidemiologic exposures of importance in the transplant recipient can be divided into four overlapping categories: (1) donor-derived infections, (2) recipient-derived infections, (3) community-derived exposures, and (4) nosocomial exposures (Table 31.1).

Donor-Derived Infections

Diverse donor-derived infections have been recognized in transplant recipients. Some of these infections are latent (e.g., viral, parasitic), whereas others are active (e.g., bacteremia, fungemia) in the donor at the time of procurement. Frequent pathogens and endemic organisms causing

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TABLE 31.1   Significant Epidemiologic Exposures Relevant to Transplantation

DONOR-DERIVED

Viral

Herpesvirus group (CMV, EBV, HHV-6, HHV-7, HHV-8, HSV)
Hepatitis viruses (HBV, HCV)
Retroviruses (HIV, HTLV-I/II)
Others (rabies, LCMV, WNV)

Bacteria

Gram-positive and gram-negative bacteria (*Staphylococcus, Pseudomonas,* Enterobacteriaceae)
Mycobacteria (tuberculous and nontuberculous)
Nocardia species

Fungi

Candida species
Aspergillus
Endemic fungi (*Cryptococcus neoformans*)
Geographically restricted fungi (*Histoplasma capsulatum, Coccidioides immitis, Blastomyces dermatitidis, Paracoccidioides brasiliensis*)

Parasites

Toxoplasma gondii
Trypanosoma cruzi

NOSOCOMIAL EXPOSURES[a]

Methicillin-resistant *Staphylococcus aureus*
Vancomycin-resistant enterococci
CRE and ESBL gram-negative bacilli
Aspergillus species
Non-*albicans Candida* species

COMMUNITY EXPOSURES[a]

Foodborne and water-borne (*Listeria monocytogenes, Salmonella, Cryptosporidium*, hepatitis A, *Campylobacter*)
Respiratory viruses (RSV, influenza, parainfluenza, adenovirus, metapneumovirus)
Common viruses, often with exposure to children (coxsackievirus, parvovirus, polyomavirus, papillomavirus)
Atypical respiratory pathogens (*Legionella, Mycoplasma, Chlamydia*)
Geographically restricted fungi, *Cryptococcus, Pneumocystis jirovecii*
Parasites (often remote) (*Strongyloides stercoralis, Leishmania, T. gondii, T. cruzi*)
Amoeba (*Naegleria fowleri, Balamuthia mandrillaris*)

CMV, cytomegalovirus; *CRE*, carbapenem-resistant Enterobacteriaceae; *EBV*, Epstein–Barr virus; *ESBL*, extended-spectrum beta-lactamase; *HBV*, hepatitis B virus; *HCV*, hepatitis C virus; *HHV*, human herpesvirus; *HIV*, human immunodeficiency virus; *HSV*, herpes simplex virus; *HTLV*, human T cell lymphotropic virus; *LCMV*, lymphocytic choriomeningitis virus; *RSV*, respiratory syncytial virus.
[a]Colonization and infection of the recipient in advance of transplantation may occur because of these potential pathogens.

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significant morbidity in recipients form the basis of screening paradigms for organ donors.[5–7] Bloodstream infections (with bacteria or yeast) in donors at the time of donation can cause local (abscess) or systemic infections, and, importantly, may adhere to anastomotic sites (vascular, urinary) to produce leaks or mycotic aneurysms.

Transmission of some donor-derived viral infections are common and expected, including cytomegalovirus (CMV) and Epstein–Barr virus (EBV), and are associated with specific syndromes in transplant recipients (see section on selected infections of importance). The greatest risk of viral infections is transmission from seropositive donors (latent infection) to seronegative (immunologically naïve) recipients (or D+/R−). Some viruses demonstrate accelerated progression (lymphocytic choriomeningitis virus [LCMV], rabies, West Nile virus [WNV]) in transplant recipients. Latent infections, such as tuberculosis, toxoplasmosis, or strongyloidiasis, may activate many years after the initial, often unrecognized exposures.

Donor screening for transplantation is limited by the available technology and by time constraints within which organs from deceased donors must be used (discussed later).[5,8,9] Routine screening of donors relies on history, and both antibody detection (serologic tests) and nucleic acid testing (NAT) for common infections. Risk factors for infection in the donor are often unknown. As a result, transmission may occur from seronegative donors with active viral or other exposures (before seroconversion in the "window period") or with viral loads below the limits of detection by the NAT selected. This risk has been demonstrated by clusters of donor-derived *Trypanosoma cruzi* (Chagas' disease), rabies virus, WNV, and LCMV infections in organ transplant recipients.[7,10–13] NAT for donor screening (e.g., for human immunodeficiency virus [HIV], hepatitis B virus [HBV], hepatitis C virus [HCV], WNV) has the capacity to reduce the window period between exposure and pathogen detection over serologic tests albeit with some risk for false-positive assays given heightened assay sensitivity.[14–18]

Given the risk of transmission of infection from the organ donor to recipients, certain syndromes should be considered relative contraindications to organ donation. Because kidney transplantation is typically elective surgery, it is reasonable to avoid donation from individuals with unexplained fever, rash, or infectious syndromes, including meningitis or encephalitis. At some centers, transplantation from donors with untreated HCV or HIV (to HIV-positive recipients) infections is undertaken. Common criteria for exclusion of organ donors are listed in Table 31.2.

Recipient-Derived Exposures

Recipient-derived exposures generally reflect colonization or latent infections that reactivate during immunosuppression.[19] Certain common infections are recognized during the evaluation of the transplant candidate, including HBV, HCV, and HIV. It is necessary to obtain a careful history of prior infections, travel, and exposures to guide preventive strategies and empirical therapies. Notable among these infections are mycobacterial infection (including tuberculosis), strongyloidiasis, viral infections (herpes simplex virus [HSV] and varicella-zoster

virus [VZV] or shingles), histoplasmosis, coccidioidomycosis, and paracoccidiomycosis (Fig. 31.1). Vaccination status should be evaluated (childhood vaccines, tetanus, HBV, influenza, pneumococcus); vaccines not previously administered should be considered in advance of

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TABLE 31.2 Common Infectious Exclusion Criteria for Organ Donors[a]

CENTRAL NERVOUS SYSTEM INFECTION

Unknown or untreated infection of central nervous system (encephalitis, meningitis)
Herpes simplex encephalitis or other encephalitis
History of JCV infection
WNV infection
Cryptococcal infection
Rabies
Creutzfeldt–Jakob disease
Other fungal or viral encephalitis
Amoebic encephalitis

DISSEMINATED AND UNTREATED INFECTIONS

HIV (serologic or molecular; may be considered for HIV-positive recipient)
HSV (with viremia), acute EBV (mononucleosis)
Serologic or molecular evidence of HTLV-I/II
Active hepatitis A (may consider HBV and HCV-infected donors for appropriate recipients)
Parasitic infections (*Trypanosoma cruzi, Leishmania donovani, Strongyloides stercoralis, Toxoplasma gondii*)

INFECTIONS DIFFICULT TO TREAT ON IMMUNOSUPPRESSION

Active tuberculosis
SARS, MERS
Untreated pneumonia
Untreated bacterial or fungal sepsis (e.g., candidemia)
Untreated syphilis
Multisystem organ failure resulting from overwhelming sepsis, gangrenous bowel

[a]These must be considered in the context of the individual donor/recipient.
EBV, Epstein–Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; HTLV, human T cell lymphotropic virus; MERS, Middle East respiratory syndrome; SARS, severe acute respiratory syndrome.

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transplantation because immune response is likely to be more robust, and live virus vaccines are generally contraindicated after transplantation (Table 31.3). Dietary habits also should be considered, including the use of well water (*Cryptosporidium*) and consumption of uncooked meats (*Salmonella, Listeria,* hepatitis E) and unpasteurized dairy products (*Listeria*).

Community Exposures

Common exposures in the community are often related to contaminated food and water ingestion; exposure to infected family members or coworkers; or exposures related to hobbies, travel, or work. Infection caused by common respiratory viruses (influenza, parainfluenza, respiratory syncytial virus [RSV], adenovirus, and metapneumovirus) and by more atypical pathogens (HSV) carry the risk of viral pneumonia and increased risk of bacterial or fungal superinfections. Community (contact or transfusion-associated) exposure to CMV and EBV may produce severe primary infection in the nonimmune host. Recent and remote exposures to endemic, geographically restricted systemic mycoses (*Blastomyces dermatitidis, Coccidioides immitis, Histoplasma capsulatum,* and *Paracoccidioides brasiliensis*) and *Mycobacterium tuberculosis* can result in localized pulmonary, systemic, or metastatic infection. Asymptomatic *Strongyloides stercoralis* infection may activate more than 30 years after initial exposure as a result of immunosuppressive therapy (see Fig. 31.1). Such reactivation can result in either a diarrheal illness and parasite migration with hyperinfection syndrome (characterized by hemorrhagic enterocolitis, hemorrhagic pneumonia, or both) or disseminated infection with accompanying (usually) gram-negative or polymicrobial bacteremia or meningitis. Gastroenteritis secondary to *Salmonella, Cryptosporidium,* and a variety of enteric viruses (e.g., norovirus) can result in persistent infection, with more severe and prolonged diarrheal disease and an increased risk of primary or secondary bloodstream invasion and metastatic infection.[20]
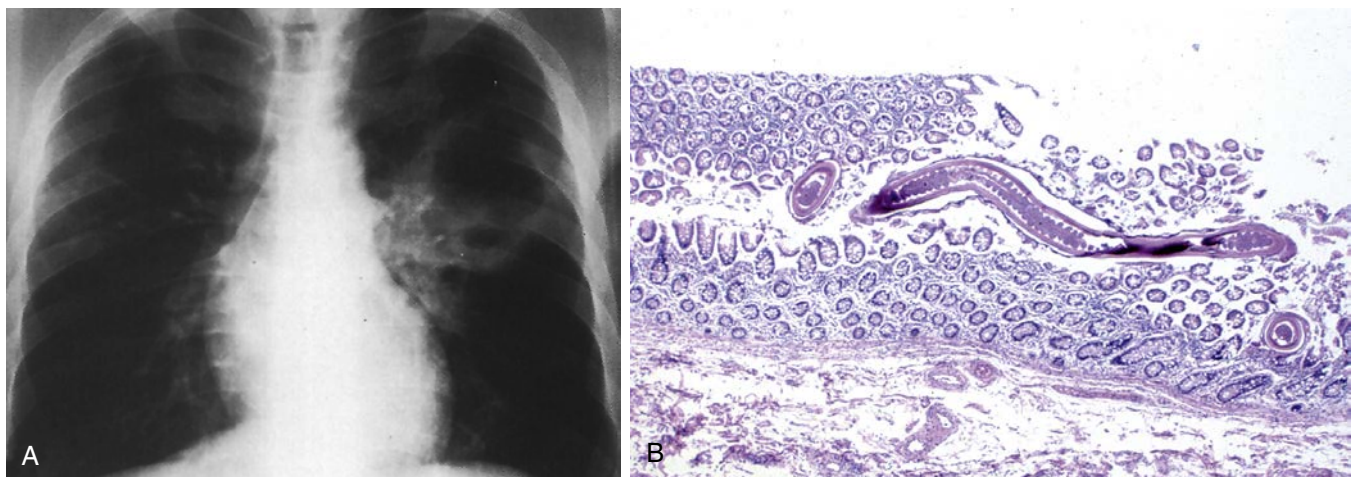
Fig. 31.1 Simultaneous *Pneumocystis* pneumonia and bacterial lung abscess secondary to coinfection by *Strongyloides stercoralis* in a Vietnamese kidney transplant recipient. (A) Chest radiograph shows a lung abscess secondary to *Enterobacter* species. Bronchoscopic examination also revealed simultaneous *Pneumocystis jirovecii* and *S. stercoralis* infections. Migration of *Strongyloides* across the wall of the gastrointestinal tract during immunosuppression (hyperinfection) is associated with systemic signs of sepsis and central nervous system infection (parasitic and bacterial). (B) *S. stercoralis* from the lung of the same patient.

TABLE 31.3 Vaccinations to Consider Before Transplantation[a]

Measles/mumps/rubella (MMR)
Diphtheria/tetanus/pertussis (DTP)
Poliovirus
Haemophilus influenzae b (Hib)
Hepatitis B, Hepatitis A
Pneumococcus
Influenza (subunit vaccine)
Varicella (Live, attenuated vaccine; zoster vaccine recombinant, adjuvanted under study)

[a]Live virus vaccinations are generally precluded in immunosuppressed hosts.

Nosocomial Exposures

Nosocomial infections are of increasing importance. Organisms with significant multidrug antimicrobial resistance (MDRO) are present in most medical centers, including enterococci that are resistant to vancomycin, linezolid, daptomycin and/or quinupristin/dalfopristin; methicillin-resistant staphylococci; gram-negative bacteria producing extended-spectrum beta-lactamases (ESBL) and carbapenemases (CRE); and fluconazole-resistant *Candida* species (see Table 31.1).[21,22] A single case of nosocomial *Aspergillus* infection in an immunocompromised host in the absence of a clear epidemiologic exposure should be viewed as a failure of infection control practices. Antimicrobial misuse and inadequate infection control practices have caused increased rates of *Clostridium difficile* colitis. Outbreaks of infections secondary to *Legionella* have been associated with hospital plumbing and contaminated water supplies or ventilation systems. Nosocomial spread of *Pneumocystis jirovecii* between immunocompromised patients has been documented.[23,24] Respiratory viral infections may be acquired from medical staff and should be considered among the causes of fever and respiratory decompensation in hospitalized or institutionalized immunocompromised individuals. Each nosocomially acquired infection should be investigated to ascertain the source and to prevent subsequent infections.

NET STATE OF IMMUNOSUPPRESSION

The net state of immunosuppression is a conceptual measure of the risk factors for infection in an individual, including immunosuppressive medications and iatrogenic conditions (Table 31.4). Among the most important are as follows:

1. The specific immunosuppressive therapy, including dose, duration, and sequence of agents (Table 31.5)
2. Technical difficulties during transplantation resulting in an increased incidence of leaks (blood, lymph, urine) and fluid collections, devitalized tissue, poor wound healing, and prolonged use of surgical drainage catheters
3. Prolonged instrumentation, including airway intubation and use of vascular access devices (e.g., dialysis catheters)
4. Prolonged use of broad-spectrum antibiotics
5. Renal or hepatic dysfunction, or both (in addition to graft dysfunction)
6. Presence of infection with an immunomodulating virus, including CMV, EBV, HBV, HCV, or HIV

Specific immunosuppressive agents are associated with increased risk for certain infections (see Table 31.5).

TABLE 31.4 Factors Contributing to the Net State of Immunosuppression

Immunosuppressive therapy: type, temporal sequence, intensity, cumulative dose
Prior therapies (chemotherapy and antimicrobials)
Mucocutaneous barrier integrity (catheters, lines, drains)
Neutropenia, lymphopenia (often drug-induced)
Underlying immunodeficiencies
Autoimmune diseases
Hypogammaglobulinemia from proteinuria or drug therapy
Complement deficiencies
Other disease states (HIV, lymphoma/leukemia)
Metabolic conditions (uremia, malnutrition, diabetes, cirrhosis)
Viral infections (CMV, HBV, HBC, RSV)
Graft rejection and treatment
Cancer/cellular proliferation

CMV, cytomegalovirus; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; RSV, respiratory syncytial virus.

TABLE 31.5 Immunosuppression and Common Infections

Agent	Common Infections/Effects
Antilymphocyte globulins (lytic) and alloimmune response	Activation of latent viruses, fever, cytokines
Anti-CD20 antibody	Unknown to date
Plasmapheresis	Encapsulated bacteria
Corticosteroids	Bacteria, *Pneumocystis jirovecii,* HBV, HCV
Azathioprine	Neutropenia, papillomavirus (?)
Mycophenolate mofetil	Early bacterial infection, late CMV (?)
Calcineurin inhibitors	Enhanced viral replication (absence of immunity), gingival infection, intracellular pathogens
mTOR inhibitors	Poor wound healing, idiosyncratic pneumonitis syndrome
Belatacept	Posttransplant lymphoproliferative disorder

CMV, cytomegalovirus; HBV, hepatitis B virus; HCV, hepatitis C virus; mTOR, mammalian target of rapamycin.
The question mark indicates possible side effect in some literature.

Assessment of the overall degree of immune compromise remains difficult. The combination of organ dysfunction, immunosuppression, viral infections, nutritional status, technical factors, and other factors in infectious risk resists quantification. Measures of pathogen-specific (i.e., cellular) immune function are useful in guiding prophylaxis for specific infections in individuals. Commercialized assays exist for CMV and tuberculosis including interferon-γ-release assays (IGRA), ELISpot, major histocompatibility complex (MHC)-tetramer staining, or intracellular cytokine staining. Low serum antibody levels correlate with the overall risk of infection but specific cutoff values and indications for replacement therapy are lacking.[25,26] Few data exist on functional immune reconstitution after T- or B-lymphocyte depletion or with costimulatory blockade. Recent data support the importance of genetic polymorphisms among transplant recipients and risk of microbial colonization and infection.[27–29]

Timeline of Infection

With standardized immunosuppressive regimens, the most common infections vary in a predictable pattern depending on the time elapsed since transplantation (Fig. 31.2). This is
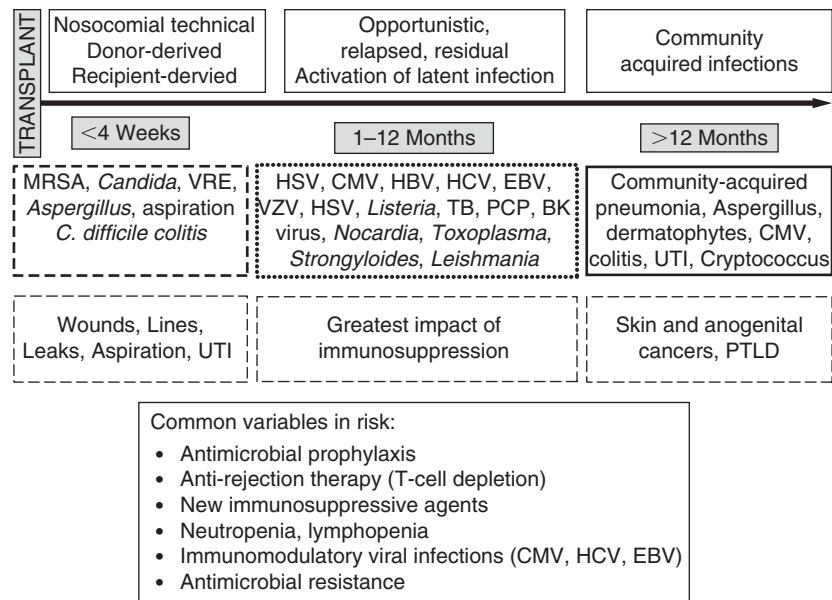
Fig. 31.2 The timeline of posttransplantation infections. Infection after transplantation tends to occur in a predictable pattern based on the epidemiologic exposure of the host and the nature of immune deficits. Patients with infections falling outside the usual patterns suggest unusual exposures or excessive immunosuppression. BKV, BK virus; CMV, cytomegalovirus; EBV, Epstein–Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HSV, herpes simplex virus; MRSA, methicillin-resistant Staphylococcus aureus; PJP, Pneumocystis jirovecii pneumonia; PTLD, posttransplant lymphoproliferative disorder; TB, tuberculosis; UTI, urinary tract infection; VRE, vancomycin-resistant enterococcus; VZV, varicella-zoster virus.

primarily a reflection of changing risk factors over time, including surgery and hospitalization, tapering of immunosuppression, acute and chronic rejection, and exposure to infections in the community.[2,30] The predicted pattern of infection changes with alterations in the immunosuppressive regimen (e.g., increased steroids for graft rejection), intercurrent viral infections, neutropenia (drug toxicity), graft dysfunction, or significant epidemiologic exposures (travel or food). The timeline remains a useful starting point for the differential diagnosis of infection after transplantation, although it is altered by the introduction of new immunosuppressive agents and patterns of use, including reduced use of corticosteroids and calcineurin inhibitors, increased use of antibody-based (induction) therapies or sirolimus, routine antimicrobial prophylaxis, improved molecular assays, antimicrobial resistance, transplantation of HIV-infected and HCV-infected individuals, and broader epidemiologic exposures from work or travel.

There are three overlapping periods of risk for infection after transplantation (see Fig. 31.2), each associated with differing patterns of common pathogens, as follows[2]:

1. The perioperative period to approximately 4 weeks after transplantation, reflecting surgical and technical complications and nosocomial exposures
2. The period from 1 to 12 months after transplantation (depending on the rapidity of taper of immunosuppression, the use of antilymphocyte "induction" therapy, and deployment of prophylaxis), reflecting intensive immunosuppression with viral activation and opportunistic infections
3. The period beyond the first year after transplantation, reflecting community-acquired exposures and some unusual pathogens based on the level of maintenance immunosuppression

The timeline can be used in a variety of ways: (1) to establish a differential diagnosis for a transplant patient suspected to have infection; (2) to provide a clue to the presence of an excessive environmental hazard for the individual, either within the hospital or in the community; and (3) to serve as a guide to the design of preventive antimicrobial strategies. Infections occurring outside the usual period or of unusual severity suggest either an intense epidemiologic exposure or excessive immunosuppression.

The prevention of infection must be linked to the risk for infection at various times after transplantation. Table 31.6 outlines some routine preventive strategies, keeping in mind that such strategies serve only to delay the onset of infection in the face of epidemiologic pressure. Use of antimicrobial prophylaxis, vaccines, and behavioral modifications (e.g., routine hand washing or advice against digging in gardens without masks) may result in a "shift to the right" of the infection timeline, unless the intensity of immunosuppression is reduced or immunity develops.

FIRST PHASE (FIRST MONTH AFTER TRANSPLANTATION)

During the first month after transplantation, three types of infection occur. The first is infection or colonization present in the recipient before transplantation that emerges in the setting of surgery and immunosuppression. Pretransplantation pneumonia and vascular access infections are common examples of this type of infection. Colonization of the recipient with resistant organisms that infect intravenous catheters or surgical drains also is common (e.g., methicillin-resistant *Staphylococcus aureus* [MRSA]). All infection should be controlled or eradicated to the degree possible before transplantation.

The second type of early infection is donor-derived. This may be nosocomially derived (resistant gram-negative bacilli and *S. aureus* or *Candida* species) colonization during the donor's hospitalization, secondary to systemic infection

TABLE 31.6   Renal Transplantation: Routine Antimicrobial Protocols

A. *PNEUMOCYSTIS JIROVECII* PNEUMONIA (PJP) AND GENERAL ANTIBACTERIAL PROPHYLAXIS

REGIMEN

- One single-strength TMP-SMX tablet (containing 80 mg trimethoprim, 400 mg sulfamethoxazole) orally daily for a minimum of 4–6 months post-transplantation. Patients infected with cytomegalovirus (CMV), with chronic rejection, or with recurrent infections are maintained on lifelong prophylaxis. A thrice-weekly regimen of TMP-SMX prevents PJP, but does not prevent other infections (e.g., urinary tract infection, *Nocardia, Listeria, Toxoplasma,* and other gastrointestinal and pulmonary infections).

ALTERNATIVE REGIMEN

- For patients proven not to tolerate TMP-SMX, alternative regimens include: (1) a combination of atovaquone, 1500 mg orally daily with meals, plus levofloxacin, 250 mg orally daily (or equivalent fluoroquinolone without anaerobic activity); (2) pentamidine, 300 mg intravenously or inhaled every 3–4 weeks; or (3) dapsone, 100 mg orally daily twice weekly, with or without pyrimethamine. Each of these agents has toxicities that must be considered (e.g., hemolysis in G6PD-deficient hosts with dapsone). None of these alternative programs offers the same broad protection of TMP-SMX.

B. CYTOMEGALOVIRUS AND HERPESVIRUS PROPHYLAXIS[a,b]

CMV UNIVERSAL ANTIVIRAL PROPHYLAXIS (KIDNEY OR PANCREAS RECIPIENTS)

Donor (D) and Recipient (R) CMV serologic status +/– T-cell depletion in induction therapy	Possible Regimen	Monitoring (Viral Load NAT)
D+/R–with induction using T cell depletion (Highest risk)	Valganciclovir 900 mg po × QD (or IV ganciclovir 5 mg/kg IV until taking po) (corrected for renal function) for 6 months	Monthly for 6 months after discontinuation of therapy[a]
D+/R– without T cell depletion (costimulatory blockade) (High risk)	Valganciclovir 900 mg po × QD (or IV ganciclovir 5 mg/kg IV until taking po) (corrected for renal function) for 3–6 months	Monthly for 6 months after discontinuation of therapy[a]
R+ without T cell depletion (costimulatory blockade) (Intermediate risk)	Oral valganciclovir (900 mg/day corrected for renal function) × 3 months or preemptive therapy	Symptoms only
R+ with T cell depletion or desensitization, (D– at Intermediate risk) (D + at Higher risk)	Oral valganciclovir (900 mg/day corrected for renal function) × 3–6 months or preemptive therapy	Symptoms only
D–/R– (Lowest risk) Target HSV/VZV	Oral famciclovir 500 mg po qd × 3–4 months (or valacyclovir 500 bid or acyclovir 400 tid); Leukocyte-filtered blood	Symptoms, fever/neutropenia

Neutropenia: The doses of antiviral therapies are not reduced for neutropenia. Formal creatinine clearance measurement may be useful in dose adjustment.
Alternatives to valganciclovir: High dose valacyclovir (≥8 g/day)—compliance is difficult and efficacy not well studied; po ganciclovir (3 g/day)—lower bioavailability.
First dose of ganciclovir is often intravenous but valganciclovir may be used if taking oral medications. All antiviral agents adjusted for renal function. For abnormal renal function, formal creatinine clearance measurement may be indicated. The dose of antiviral therapy is generally not reduced for neutropenia. Consider other options first.
Antifungal Prophylaxis: Mucocutaneous candidiasis can be prevented with oral clotrimazole or nystatin 2–3 times per day during corticosteroid therapy or in the face of broad-spectrum antibacterial therapy and in diabetic transplant patients. Fluconazole,.200 mg/day for 10–14 days, is used to treat prophylaxis failures. Routine prophylaxis with fluconazole is used for pancreas and kidney–pancreas transplants. Other prophylaxis is determined based on the presence or absence of colonization or other risk factors for fungal infection.
[a]**Hybrid Prophylaxis:** Many centers prefer universal prophylaxis for highest risk kidney recipients (D+/R– or R+ with lymphocyte depletion) and preemptive therapy for lower risk groups.
[b]**Preemptive Therapy:** Preemptive therapy requires a carefully organized monitoring program and patient compliance. Either a molecular CMV viral load test or a pp65 antigenemia assay may be used for monitoring. Monitoring should be performed once weekly after transplantation for 12–24 weeks. Infections indicated by positive assays are treated with either oral valganciclovir or intravenous ganciclovir. Therapy is continued at least until viremia is undetectable.
D, donor serology; R, recipient serology; NAT, nucleic acid test normalized to the World Health Organization international standard.

in the donor (e.g., line infection), or contamination during the organ procurement process. Active infections may be transmitted from donor to recipient and emerge earlier than normally predicted (e.g., HSV, tuberculosis, histoplasmosis). Most recent clusters of donor-derived infection have been the result of unfortunate timing—a donor who acquired acute infection (HIV, WNV, rabies, or LCMV) before and unrelated to the cause of death.

The third and most common source of infection in the early period is related to the transplant procedure. These infections include surgical wound infections, pneumonia (aspiration), bacteremia associated with vascular access or surgical drainage catheters, urinary tract infections, and superinfection of fluid collections—leaks of vascular or urinary anastomoses or of lymphoceles. These are nosocomial infections and, as such, may carry the same antimicrobial-resistant pathogens observed in nonimmunosuppressed

patients undergoing comparable surgery. Given immunosuppression, the signs of infection may be subtle and the severity or duration is usually increased. Thus bowel perforation may be clinically silent, marked only by tachycardia, a rising white blood cell count, abnormal liver function tests, or graft dysfunction. The technical skill of the surgeons and meticulous postoperative care (i.e., wound care and proper maintenance and timely removal of endotracheal tubes, vascular access devices, and drainage catheters) determine the degree of risk for these infections. Another important infection during this period is *Clostridium difficile* colitis.[31,32]

Limited perioperative antibiotic prophylaxis (i.e., from a single dose to 24 hours of an antibiotic such as cefazolin or amoxicillin-clavulanate) is usually adequate for renal transplantation with additional coverage required for known risk factors (e.g., prior colonization with MRSA). For pancreas transplantation, additional perioperative prophylaxis

against yeasts is useful with fluconazole, mindful of potential increases in sirolimus and calcineurin inhibitor levels when used concomitantly with azole antifungal agents.

Opportunistic infections are notably absent in the first month after transplantation, even though the daily doses of immunosuppressive drugs may be greatest during this time. The implication of this observation is important because it suggests the daily dose of immunosuppressive drugs is less important than the cumulative dose (i.e., the "area under the curve") for determining the true state of immunosuppression. The net state of immunosuppression during the first month after transplant is not great enough to support opportunistic infections, unless exposure has been excessive. Accordingly, the occurrence of a single case of opportunistic infection in this period should trigger an epidemiologic investigation for an environmental hazard.

SECOND PHASE (1–12 MONTHS AFTER TRANSPLANTATION)

The second phase of infection was traditionally 1 to 3 months, but has been extended because of two main factors: successful use of prophylaxis or monitoring programs targeting CMV and the herpesviruses, *Pneumocystis,* urinary tract infections, and HBV, and intensification of immunosuppression using more potent agents or antibody-based induction therapies with prolonged effects on immune function (see Table 31.5).[1,2] Infection in the transplant recipient 1 to 12 months after transplantation has one of three causes:

1. Infection from the perisurgical period, including relapsed *C. difficile* colitis, inadequately treated pneumonia, or infection related to a technical problem (e.g., urine leak, hematoma). Fluid collections in this setting generally require drainage.
2. Viral infections including CMV, HSV, VZV, human herpesvirus (HHV)-6 or HHV-7, EBV, HBV, HCV, and HIV. Viruses are prominent given the importance of T cell function in antiviral control and the disproportionate degree of T cell inhibition by most immunosuppressive regimens. Furthermore, these viruses are systemically immunosuppressive, predisposing to opportunistic infection or acceleration of other infections and, via chronic immune stimulation, predispose to graft rejection. Useful therapies are now available for most of these pathogens. The herpesvirus infections are lifelong and tissue-associated, transmitted with the allograft from seropositive donors. Other common viral pathogens of this period include BK polyomavirus (in association with allograft dysfunction or polyomavirus-associated nephropathy [PyVAN]) and community-acquired respiratory viruses (adenovirus, influenza, parainfluenza, RSV, metapneumovirus). Bacterial and fungal superinfection of virally infected hosts is common.
3. Opportunistic infections secondary to *P. jirovecii, L. monocytogenes, Toxoplasma gondii, Cryptococcus neoformans, Nocardia, Aspergillus,* and other agents

In this period, the stage also is set for the emergence of a subgroup of patients—the "chronic ne'er do well"—the patient who requires higher than usual levels of immunosuppression to maintain graft function, who had a poor technical outcome of transplantation (leaks or vascular issues) or poor graft function, or who has persistent viral or other infections (e.g., *C. difficile* colitis), which predict long-term susceptibility to other infections (third phase, discussed next). Such patients may benefit from prolonged (lifelong) prophylaxis (antibacterial, antifungal, antiviral, or a combination) to prevent life-threatening infection.

Opportunistic infections reflect the immunosuppressive regimen used, individual epidemiology, and the presence or absence of immunomodulating viral infection. Viral pathogens (and rejection) are responsible for most febrile episodes that occur in this period. Anti-CMV strategies and trimethoprim/sulfamethoxazole (TMP-SMX) prophylaxis are effective in decreasing the risk of infection. TMP-SMX prophylaxis effectively prevents *Pneumocystis* pneumonia and reduces the incidence of urinary tract infection and urosepsis, *L. monocytogenes* meningitis, *Nocardia* species infection, and *T. gondii.*

THIRD PHASE (MORE THAN 12 MONTHS AFTER TRANSPLANTATION)

Recipients who underwent transplantation more than a year previously can be divided into three groups in terms of infectious risk. Most transplant recipients (70%–80%) have a technically good procedure with satisfactory allograft function, reduced immunosuppression, and absence of chronic viral infection. These patients resemble the general community in terms of infection risk, with community-acquired respiratory viruses constituting the major risk. Occasionally, such patients develop primary CMV infection (socially acquired) or infections related to underlying diseases (e.g., skin infections in diabetics).

A second group of patients has chronic viral infection, which may produce end organ damage (e.g., BK polyomavirus leading to fibrosis, HCV leading to cryoglobulinemia and cirrhosis, CMV with chronic graft rejection) or malignancy (e.g., posttransplantation lymphoproliferative disease (PTLD) secondary to EBV, skin or anogenital cancer related to papillomaviruses). In the absence of specific and effective antiviral therapy, these patients often suffer graft rejection with the reduced intensity of immunosuppression.

A third group of patients has unsatisfactory allograft function and suffers the ravages of renal dysfunction, often despite intensified immunosuppression used to preserve graft function. Declining allograft function may be a result of underlying disease progression (atherosclerosis, IgA, or diabetes), calcineurin inhibitor toxicity, or humoral and cellular graft rejection. Thus these patients are overimmunosuppressed relative to the risk of infection. These patients may benefit from lifetime maintenance TMP-SMX and often fluconazole prophylaxis. In this group, one also should consider organisms more commonly associated with immune dysfunction of acquired immunodeficiency syndrome (AIDS; *Bartonella, Rhodococcus, Cryptosporidium,* and microsporidia) and invasive fungal pathogens (*Aspergillus, Mucorales,* and dematiaceous or pigmented molds). Even minimal clinical signs or symptoms warrant careful evaluation in this group of high-risk patients.

Assessment of Infectious Diseases in Recipients and Potential Donors Before Transplantation

Guidelines for pretransplant screening have been the subject of several publications, including a consensus conference of the Immunocompromised Host Society, the American Society for Transplantation Clinical Practice Guidelines for the evaluation of kidney transplant candidates, and the American Society of Transplant Surgeons Clinical Practice Guidelines for the evaluation of living kidney transplant donors.[19,33,34]

TRANSPLANT DONOR

Deceased Donor Evaluation

A crucial challenge in screening deceased organ donors is the narrow time frame for the evaluation. A useful organ must be procured and implanted before some microbiologic assessments have been completed. Thus bacteremia or fungemia may not be detected until after transplantation has been performed. Such infections generally have not resulted in transmission of infection if the infection has been adequately treated before procurement using antimicrobial agents to which the organism is susceptible for an appropriate duration. In recipients of tissues from 95 bacteremic donors, a mean of 3.8 days of effective therapy after transplantation prevented transmission of susceptible pathogens (in an era of reduced antimicrobial resistance). Surveillance with additional courses of therapy in the recipient are employed, targeting known donor-derived pathogens.[2,35] Bacterial meningitis must be treated with antibiotics that

penetrate the cerebrospinal fluid before organ procurement. Individuals with unidentified and untreated causes of meningoencephalitis or sepsis should not be used as organ donors. Donor-derived infections caused by *Candida* species have resulted from organ contamination or candidemia at the time of procurement.[36,37] Susceptibility testing of the isolate and prolonged treatment (2–4 weeks) with effective agents to avoid pyelonephritis, abscess formation, mycotic aneurysm, or candidemia in the recipient is recommended. Vascular involvement by *Candida* species in the recipient requires at least 6 weeks of therapy. Certain active infections (CMV, VZV, HSV, EBV, or HCV) may be unsuspected even in the seropositive donor and require NAT for diagnosis. Likewise, the donor's clinical, social, and medical histories are essential to reducing the risk of such infections. Known infection should be treated before procurement if possible. See previous discussion of unrecognized donor pathogens. Major exclusion criteria are outlined in Table 31.2.

Living Donor Evaluation

The living donor procedure should be considered elective, and the evaluation should be completed and infections treated before donation.[38] An interim history must be taken at the time of surgery to assess the presence of new infections since the initial donor evaluation. Intercurrent infections (flu-like illness, headache, confusion, myalgias, cough) might be the harbinger of important infection (WNV, severe acute respiratory syndrome [SARS], *Trypanosoma cruzi*). Live donors undergo a battery of serologic tests (Table 31.7), purified protein derivative (PPD) skin test or tuberculosis interferon-γ release assay, and, if indicated, chest radiograph. The testing must be individualized, based on unique risk factors (e.g., travel). Of note in the kidney

TABLE 31.7 Pretransplant Evaluation of Living Donors

Pathogen	Laboratory Test	Quantitative Molecular Test Available	All Patients	Patients With Exposure to Endemic Area
CMV	Serologies	X	X	
HSV	Serologies	X	X	
EBV	Serologies		X	
HIV	Serologies	X	X	
HBV	Serologies including: HBV surface antigen and HBV surface antibody	X	X	
HCV	Serologies	X	X	
Treponema pallidum	RPR or VDRL test		X	
Toxoplasma gondii	Serologies			X
Strongyloides stercoralis	Serologies Stool ova and parasite examination			X
Leishmania	Serologies			X
Trypanosoma cruzi	Serologies Blood smear			X
Shistosomiasis	Urine ova and parasite examination with or without endoscopy			X
Histoplasma capsulatum	Serologies			X
Coccidioides immitis	Serologies			X
Bacteria and yeasts	Urinalysis and culture		X	
Mycobacterium tuberculosis	Skin test or IGRA		X	
Latent and active pulmonary infections	Chest x-ray (routine)		X	

anti-HBs, antibody to hepatitis B surface antigen; CMV, cytomegalovirus; EBV, Epstein–Barr virus; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; IGRA, interferon gamma release assay; RPR, rapid plasma reagin; VDRL, venereal disease research laboratory; VZV, varicella-zoster virus.

transplant recipient is the exclusion of urinary tract infections (including both bacteria and yeasts) and bacteremia at the time of donation. The US Public Health Service suggests rescreening potential donors as close to donation as is feasible, using NAT for HIV, HCV, and HBV.

Special Infectious Risks and Organ Procurement

Tuberculosis. *Mycobacterium tuberculosis* from the donor represents approximately 4% of reported post-transplant tuberculosis cases.[39,40] Much higher rates occur in endemic regions.[41,42] Active disease should be excluded in PPD-positive donors with chest radiograph, sputum cultures, and chest computed tomography (CT) if the chest radiograph is abnormal. Urine acid-fast bacillus cultures may be useful in a PPD-positive kidney donor. Isoniazid prophylaxis of the recipient should be considered for untreated PPD-positive donors. Factors favoring prophylaxis include a donor from an endemic region, high-risk social environment, or use of a high-dose steroid regimen in the recipient.

Parasites. Chagas' disease (*Trypanosoma cruzi*) has been transmitted by transplantation in endemic areas and more recently in the US.[7,43] Schistosomiasis and *Strongyloides stercoralis* are generally recipient-derived. Malaria and leishmaniasis have been rarely transmitted with allografts.

Viral Infections Other Than Cytomegalovirus. EBV infection is a major risk for development of PTLD. The risk is greatest in the EBV-seronegative recipient of an EBV-seropositive allograft (i.e., donor seropositive, recipient seronegative, D+/R−).[44,45] This situation is most common in pediatric transplant recipients. Other at-risk groups include adults coinfected with CMV or those receiving greater intensity of immunosuppression, notably with T cell depletion and possibly with belatacept.[46–48] Monitoring should be considered for at-risk individuals using a quantitative molecular assay for EBV.[49] EBV is also a cofactor for other lymphoid malignancies.

VZV screening should be used to identify seronegative individuals (no history of chickenpox or shingles) for vaccination before transplantation. It is likely, although unstudied, that the new herpes zoster subunit vaccine will replace live vaccine before and after transplantation. HSV screening is performed by most centers although active infection is prevented by most anti-CMV prophylaxis (except with newer agents such as maribavir and letermovir) during the posttransplant period. VZV serologic status is particularly important in nonimmune children who may be exposed at school (for antiviral or VZV immunoglobulin prophylaxis) and in adults with atypical presentations of infection (pneumonia or gastrointestinal disease). Other herpesviruses also may reactivate, with HHV-6 and HHV-7 serving as cofactors for CMV and fungal infections, and Kaposi's sarcoma-associated herpesvirus (HHV-8) causing malignancy, notably in endemic regions in South America and surrounding the Mediterranean basin.

Hepatitis screening has changed with quantitative nucleic acid test (QNAT) screening and the advent of effective antiviral therapies.[18,34,50] HBV surface antigen (HBsAg) and HBV core antibody (HBcAb) are used for screening purposes (see Chapter 32 for detailed discussion).[51] A positive HBV surface antibody titer indicates either vaccination or prior infection. HBcAb-IgM positivity suggests active HBV infection, whereas IgG positivity suggests a more remote or persistent infection. The HBsAg-negative, HBcAb-IgG-positive donor will have viral DNA in the liver but may be appropriate as a kidney donor for HBV-infected or vaccinated, and thus immune, renal recipients; quantitative viral assays for HBV should be obtained to guide further therapy.[52] The presence of HBsAg-negative, HBcAb-IgG-positive assays may be a false-positive result or reflect true, latent HBV infection.

The effect of HCV infection has changed in the era of directly active antiviral agents (DAA); evidence exists that the use of HCV-positive kidneys has clinical benefits for the recipient.[53] Pan-genotypic DAA therapies cure over 95% of HCV infections in transplantation.[50] Untreated, HCV infection progresses to cirrhosis more rapidly with immunosuppression and with CMV coinfection (see Chapter 32 for detailed discussion). Side effects of historical therapies (pegylated interferon-α and ribavirin) are increased in the transplant population. HCV therapy is initiated based on center-specific protocols and may rely on quantitative NAT for HCV ribonucleic acid (RNA) and liver function testing (see Chapter 32).

Historically, the progression of untreated HIV infection in transplant recipients is rapid. However, HIV-infected kidneys (and other organs) have been transplanted into HIV-infected recipients in South Africa and elsewhere.[54] Under the US HIV Organ Policy Equity (HOPE) Act, organs from HIV-infected donors may be transplanted into HIV+ recipients as part of a clinical trial with informed consent.[55] The first planned HIV+/HIV+ transplant in the US was performed in March 2016. Based on current criteria for recipients who are not HIV infected, donors are evaluated based on epidemiology and using fourth-generation enzyme-linked immunosorbent assay (ELISA)-NAT testing.

Human T cell lymphotropic virus I (HTLV-I) is endemic in the Caribbean and parts of Asia (Japan) and can progress to HTLV-I-associated myelopathy/tropical spastic paraparesis or to adult T cell leukemia/lymphoma. HTLV-II serologically cross-reacts with HTLV-I, but it is less clearly associated with disease. Use of organs from such donors is generally avoided; however, serologic testing does not distinguish between the two types of virus. Donor screening for HTLV in the US is no longer mandatory, but some centers continue donor screening in endemic regions or use targeted screening of donors perceived to be high risk.[56–58] WNV is a flavivirus associated with viral syndromes and meningoencephalitis and may be transmitted by blood transfusion and organ transplantation.[7,36,46] Routine screening of donors is not advocated other than in areas with endemic infection. Donors with unexplained changes in mental status or recent viral illness with neurologic signs should be avoided.

EVALUATION OF THE TRANSPLANT RECIPIENT

The pretransplant period is useful for obtaining travel, animal, environmental, and exposure histories; updating immunizations; and counseling the recipient regarding travel, food, and other infection risks. Ongoing infection must be eradicated to the degree possible before transplantation. Two forms of infection pose a special risk—bloodstream infection related to vascular access (including that for dialysis) and pneumonia, which puts the patient at high

risk for subsequent lung infection with nosocomial organisms. Several other infections are commonly encountered and should be treated and cleared before transplantation. Peritonitis must be cleared before surgery and infected peritoneal dialysis catheters removed. Urinary tract infection must be eliminated with antibiotics, with or without nephrectomy. Similarly, skin disease threatens the integrity of a primary defense against infection and should be corrected even if doing so requires the initiation of immunosuppression (e.g., to treat psoriasis or eczema) before transplantation. Finally, a history of more than one episode of diverticulitis should trigger an evaluation to determine whether colectomy is indicated before transplant.

Among important considerations in transplant recipients are strongyloidiasis, tuberculosis, and AIDS. *Strongyloides* hyperinfection syndrome (hemorrhagic enterocolitis, pneumonia, gram-negative or polymicrobic bacteremia, or meningitis) may occur more than 30 years after transplantation. Patients from endemic areas should be screened and *Strongyloides*-seropositive recipients empirically treated (ivermectin) pretransplant to prevent active disease after transplant.

The incidence of active and disseminated tuberculosis is higher in the transplant recipient than in the general population and the major antituberculous drugs are potentially hepatotoxic and some significantly interact with immunosuppressive agents.[39–41,59,60] Thus eradication of tuberculosis in transplant candidates before transplantation is preferred. Patients at greater risk of tuberculosis infection or exposure include individuals with prior history of active tuberculosis or significant signs of old tuberculosis on chest radiograph, recent tuberculin reaction conversion, known exposure to active disease, protein-calorie malnutrition, cirrhosis, other immunodeficiency, or exposures related to living conditions (e.g., in a shelter or other group housing). PPD-positive individuals from endemic regions or with high-risk exposures should be screened for active disease and treated for such if present. For those with latent infection, therapy should be initiated before transplantation although some judgment may be used as to the optimal timing of latent treatment.

HIV infection has generally been converted from a progressively fatal disease to a chronic infection controlled by complex regimens of antiviral agents or highly active antiretroviral therapy (HAART). In the pre-HAART era, organ transplantation generally was associated with a rapid progression to AIDS. Kidney transplantation in HIV-infected recipients has been associated with good outcomes in individuals with controlled HIV infection and with treatment of HCV coinfection.[61–65] After transplantation, HAART must be continued despite multiple and reciprocal drug interactions between antiretroviral and immunosuppressive medications. This necessitates experience in HIV and transplant drug management.[66] Rejection will occur more frequently than in other hosts and standard intensity of immunosuppression is required. The most significant interactions are between the calcineurin and mammalian target of rapamycin (mTOR) inhibitors and HIV protease inhibitors (PIs) and nonnucleoside analog reverse transcriptase inhibitors (NNRTIs) via the hepatic cytochrome P450 3A4 system and P-glycoprotein.[61,67,68] Adjustment in dosages and dosing intervals of immunosuppressive medications is required, and

drug levels and toxicities must be monitored closely. Some drugs (e.g., raltegravir) have fewer interactions, and the CC chemokine receptor type 5 (CCR5) receptor antagonist maraviroc may even decrease rates of graft rejection.[69,70] In vitro antiretroviral synergy occurs between sirolimus and earlier CCR5 antagonists; the use of sirolimus-based immunosuppression may increase rates of graft rejection.[71] Prophylaxis against *P. jirovecii* pneumonia (PJP), and toxoplasmosis in seronegative recipients of seropositive organs, should be continued for life, preferably using TMP-SMX.

Selected Infections of Importance

GENERAL CONSIDERATIONS

The spectrum of infection in the immunocompromised host is broad. Given the potential toxicity of antimicrobial agents and the need for rapid interruption of infection, early, specific diagnosis is essential in this population. Whereas initial, empiric therapy is broad by necessity, a rapid narrowing of the antimicrobial spectrum as data become available is essential. Advances in diagnostic modalities (e.g., CT or magnetic resonance imaging, molecular microbiologic techniques, high-throughput sequencing) greatly assist in this process, but the need for invasive procedures cannot be overemphasized because they are often required for specific microbiologic diagnosis.

Key among decisions in antiinfective therapy is whether to reduce the intensity of immunosuppression, with the understanding that the risks of such an approach are graft rejection and/or an aggressive and sometimes detrimental inflammatory response, the immune reconstitution inflammatory syndrome (IRIS), perhaps best demonstrated in patients with cryptococcal meningitis in whom a "rebound" of inflammatory responses may result in worsening symptoms and hydrocephalus despite appropriate antimicrobial therapy. For latent viral infections or tuberculosis, activation is evidence of excessive immunosuppression relative to the host's immune function. In contrast, for intercurrent bacterial or fungal infections, reductions in immunosuppression might be reversed when resolution of infection is demonstrated. The specific reduction chosen may depend on the organisms isolated (e.g., corticosteroids and bacterial infections). Similarly, reversal of some immune deficits (e.g., neutropenia, hypogammaglobulinemia) may be possible with adjunctive therapies (e.g., colony-stimulating factors or antibody therapy). Finally, coinfection with immunoregulatory viruses such as CMV is common during other active infections and should be screened for and treated.

VIRAL PATHOGENS

Cytomegalovirus

Invasive infection resulting from CMV has become less common because of the availability of effective antiviral therapies, and diagnostic and monitoring assays for the virus[72] (see Table 31.6B). Even latent infection or low-level replication has important implications for transplant outcomes, and strategies used to prevent (universal versus preemptive therapy) and treat infection vary between centers.[73] The

manifestations of CMV infection have been traditionally termed "direct" and "indirect" effects. More accurate terms might be "viremic/cytopathic" effects and "cellular/immunologic" effects. The common direct effects or clinical syndromes include:

- CMV syndrome, viremia associated with fever and neutropenia, variably associated with features of infectious mononucleosis, including hepatitis, nephritis, lymphadenitis, leukopenia, and/or thrombocytopenia
- Pneumonitis, which is often difficult to distinguish from apparently benign secretion
- Gastrointestinal invasion with esophagitis, colitis, gastritis, ulcers, bleeding, or perforation
- Hepatitis, pancreatitis, or myocarditis
- Meningoencephalitis
- Hemolytic uremic syndrome or microangiopathic thrombosis
- Chorioretinitis and central nervous system (CNS) vasculitis or encephalitis

The direct clinical manifestations of CMV infection usually occur 1 to 6 months after transplantation in the absence of prophylaxis, other than chorioretinitis. Chorioretinitis can occur at low levels of viral replication and generally later in the posttransplant course. Viremia and symptomatic infections are rare during effective antiviral prophylaxis. CMV activation may develop despite prophylaxis during intensification of immunosuppression (e.g., for rejection).

The cellular and immunologic effects of CMV infection (discussed later) are the result of the suppression of a variety of host defense mechanisms and predispose to secondary invasion by *P. jirovecii, Candida* and *Aspergillus* species, and other bacterial and fungal pathogens.[73] CMV infection also contributes to the risk for graft rejection, PTLD, acceleration of HCV coinfection, HHV-6 and HHV-7 infections, and increased risk for death.

Patterns of Transmission. Transmission of CMV in the transplant recipient occurs in one of three patterns: primary infection, reactivation infection, and superinfection.

Primary CMV Infection. The greatest risk for CMV infection is in the setting of seronegative individuals receiving grafts from latently infected, seropositive donors (D+/R−), with reactivation of virus within the graft. Over 50% of these patients become viremic in the absence of prophylaxis, often without symptoms. Many become viremic after cessation of antiviral prophylaxis, with symptomatic "late infection" occurring in up to one-third of recipients previously treated with prophylaxis.[74] Primary CMV infection is often severe and may also occur in seronegative individuals such as in children, after transfusion, or via sexual contacts in the community. The allograft may be a privileged site for viral replication because the MHC-restricted, virus-specific, cytotoxic T cells have decreased ability to eliminate virally infected cells in the presence of donor and recipient MHC mismatch.

Reactivation CMV Infection. In reactivation infection, seropositive individuals reactivate endogenous virus after transplantation (D+ or D−/R+). When conventional immunosuppressive therapy is used without antilymphocyte antibody induction treatment, approximately 10% to 15% experience direct CMV syndrome in the absence of prophylaxis with a higher rate, up to 50%, after T cell depletion therapies.[74]

CMV Superinfection. Virus derived from a seropositive donor may reactivate in a seropositive recipient (D+/R+). Blood transfusions, even if leukocyte-reduced, have a low rate (~4%) of transmission of CMV infection.[75] This observation gains importance in patients requiring significant transfusion in the perioperative setting.

Pathogenesis of Infection. Multiple factors may drive CMV activation, including the intensity of immunosuppression (notably pulsed-dosed corticosteroids), the amount of virus in the graft, the use of lytic T cell-depleting therapies, coinfections with other herpesviruses (HHV-6 and HHV-7), and graft rejection. These events share features of inflammation and fever, endothelial activation and injury, and secretion of proinflammatory cytokines, including tumor necrosis factor-α that activates intracellular NF-κB. NF-κB translocates to the cell nucleus to activate the CMV major immediate-early promoter/enhancer and viral replication.[76,77]

The risk of viral activation with graft rejection is most prominent in the D+/R− combination with the alloimmune response producing graft inflammation and injury, generally the site of greatest viral load and MHC mismatch, intensification of immunosuppression, systemic inflammation with fever, and enhanced MHC display in the allograft. Thus a bidirectional linkage exists between CMV replication and graft rejection. Reinke et al.[67] showed that 17 of 21 patients with biopsy evidence of late acute rejection demonstrated a response to antiviral therapy. Similarly, Lowance and colleagues have demonstrated that preventing CMV infection also resulted in a lower incidence of graft rejection.[73,78] The cellular and immunologic effects of CMV ("indirect effects") are as important to the immunocompromised host as invasive viral infection. The mechanisms for these effects are complex and relate to viral strategies to evade the host's responses and allow CMV-infected antigen-presenting cells to travel throughout the host and spread the virus.

Diagnosis. Clinical management of CMV, including prevention and treatment, is based on understanding the causes of CMV activation and the available diagnostic techniques. CMV cultures are no longer essential for resistance testing, which can be performed by molecular sequencing.[72,79,80] Positive CMV cultures (or shell vial culture) derived from respiratory secretions or urine are of little diagnostic value—many immunosuppressed patients secrete CMV in the absence of invasive disease. Serologic tests are useful before transplantation to predict risk but are of little value after transplantation in defining clinical disease, because seroconversion is generally delayed. Seroconversion to positive CMV IgG provides evidence that the patient has developed some degree of immunity and appears to correlate generally with T cell function.

Quantitation of the intensity of CMV viral burden has been linked to the risk for infection in transplant recipients.[74,81–84] Two types of quantitative assays have been

developed: molecular and antigen detection assays. The antigenemia assay is labor-intensive and, being semiquantitative, it is less commonly used than NAT; circulating neutrophils are immunostained for CMV early antigen (pp65) that is taken up nonspecifically as a measure of the total viral burden. QNAT is generally used for diagnosis, preemptive management strategies, and monitoring response to therapy.[85–89] CMV deoxyribonucleic acid (DNA) is generally detected earlier in whole blood compared with plasma; one specimen type and one laboratory should be used when monitoring patients. The highest viral loads often are associated with tissue-invasive disease; the lowest are associated with asymptomatic CMV infection. Multiple viral strains are often present during infection. Viral loads present during CMV syndrome vary widely. A single quantitative assay should be used consistently for monitoring each patient. A World Health Organization (WHO) International Reference Standard became available in 2010 from a clinical isolate (Merlin) with a titer of 5×10^6 IU/mL. All laboratory tests should be calibrated to the WHO International Standard with results reported as IU/mL.[90] One source of variability is different DNA extraction methods. Multiple viral genotypes may be observed, often in patients with more severe disease and in antiviral resistance. Resistance testing should be performed in the face of poor clinical and virologic response to adequate therapy for at least 10 to 14 days; responses may be delayed with high-level viremia. Multiple risk factors for drug resistance often coexist, including prolonged antiviral drug exposure; notably with inadequate dosing, lack of immunity, high-level viral replication; and intensive immunosuppression.

The advent of quantitative assays for the diagnosis and management of CMV infection has allowed noninvasive diagnosis in many patients with two important exceptions:

1. Neurologic disease, including chorioretinitis
2. Gastrointestinal disease, including invasive colitis and gastritis.

In these syndromes, CMV viral loads are often low or below detection limits. For the diagnosis of gastrointestinal CMV disease, demonstration of CMV inclusions in tissues and/or immunohistology for CMV antigens remain essential. The central role of assays is illustrated by the approach to the management of CMV risk (see Table 31.6B). The schedule for screening is linked to the risk for infection. In the high-risk patient (D+/R− or R+ with antilymphocyte globulin), after the completion of prophylaxis, monthly screening is performed to ensure the absence of viremia for 3 to 6 months. In the patient being treated for CMV infection, the assays provide an endpoint for therapy and the initiation of prophylaxis.

Cytomegalovirus Prevention. Prevention of CMV infection must be individualized for immunosuppressive regimens and the patient (see Table 31.6B).[74,91] Two strategies are commonly used for CMV prevention—universal prophylaxis and preemptive therapy.[84] Universal prophylaxis involves giving antiviral therapy to all at-risk patients after transplantation for a defined period. In preemptive therapy, QNAT assays are used to monitor patients at predefined intervals (generally weekly for weeks 1–12) to detect early disease. Positive assays result in therapy. Preemptive

therapy incurs extra costs for monitoring and coordination of outpatient care, while reducing the cost of drugs and the inherent toxicities. Prophylaxis has the possible advantage of not only preventing CMV infection during the period of greatest risk but also diminishing infections secondary to HHV-6, HHV-7, and EBV. The indirect effects of CMV (i.e., graft rejection, herpesvirus infections, opportunistic infections) also may be reduced by routine prophylaxis. In practice, neither universal prophylaxis nor preemptive therapy is perfect. Many centers use a combination of both approaches: universal prophylaxis for the highest-risk recipients (D+/R− and R+ with T cell depletion) and preemptive therapy for others. Infrequently, breakthrough disease and ganciclovir resistance have been observed with both approaches.

Given the risk of invasive infection, patients at risk of primary infection from the donor (CMV D+/R−) and seropositive patients receiving depleting anti–T-lymphocyte antibodies are generally given prophylaxis for 3 to 6 months after transplantation. Other groups are candidates for preemptive therapy if an appropriate monitoring system is in place and patient compliance is good. Current data support the use of universal prophylaxis (not preemptive therapy) in the prevention of indirect effects of CMV infection, including PTLD, opportunistic infections, allograft rejection, and mortality.[73] Increasingly, "late" disease has been observed after the completion of prophylaxis.[92,93] Thus monitoring may be useful after prophylaxis. The rate of late disease varies but is thought to be as high as 17% to 37% in D+/R− recipients, supporting the value of prophylaxis for 6 months in D+/R− renal recipients (the IMPACT study).[93]

Options for CMV prophylaxis include valganciclovir (900 mg orally once daily), oral ganciclovir (1 g three times daily), intravenous ganciclovir (5 mg/kg once daily), or high-dose oral valacyclovir (2 g four times daily)—each corrected for renal function. Valganciclovir and ganciclovir are associated with neutropenia; however, dose reduction risks breakthrough viremia and the emergence of viral resistance. Given changing renal function after transplantation and the costs of medication, many regimens employ lower doses of valganciclovir.[94,95] Such regimens should be coupled with monitoring to assure efficacy. After completion of treatment for CMV disease (see later), many centers initiate a course of secondary prophylaxis (1−3 months). An alternative is a strategy of virologic monitoring during this period.

Treatment. The standard of care for treating invasive CMV disease is 2 to 4 weeks of intravenous (IV) ganciclovir (5 mg/kg twice daily, with dosage adjustments for renal dysfunction) until a quantitative assay for CMV is negative.[91] In patients with mild to moderately severe symptoms, valganciclovir (900 mg orally twice daily corrected for renal function) may be used as an alternative. In symptomatic patients slow to respond to therapy and who are seronegative, the addition of CMV hyperimmune globulin (150 mg/kg/dose IV monthly) for 3 months is controversial, costly, and of uncertain benefit. Relapse does occur, primarily in seronegative patients, in those with high viral burdens, if not treated to the achievement of a negative quantitative assay, and in gastrointestinal disease treated with an oral regimen. Repeat endoscopy may be considered with poor

clinical response, or if other processes are present (ischemia, cancer). In practice, it is reasonable to initiate therapy with intravenous ganciclovir, monitor weekly to assure a virologic response and treat until after monitoring is negative (often two negative weekly assays). Such patients may benefit from 2 to 4 months of oral valganciclovir (900 mg daily based on creatinine clearance) administered as secondary prophylaxis after the completion of intravenous therapy. This approach has resulted in rare symptomatic relapses and has been associated uncommonly with the emergence of antiviral resistance. It may be worth measuring a formal creatinine clearance to assure adequate dosing.

The incidence of ganciclovir resistance in CMV is generally low.[79,80] The risk of resistance is greatest in D+/R− recipients with higher viral loads, who received inadequate dosing of prophylactic or therapeutic ganciclovir, more intensive immunosuppression including antilymphocyte antibody induction, and with prolonged antiviral prophylaxis. Clinically, the patient's viral load or clinical syndrome fails to respond to appropriate therapy, including a reduction in immunosuppression over 10 to 14 days. Genetic resistance testing is useful in managing resistant CMV infection. Many mutations have now been identified, including mutations in the viral UL97 (thymidine kinase) or UL54 (DNA polymerase) genes that confer ganciclovir resistance. Some of the common mutations in the UL97 gene respond to higher doses of intravenous ganciclovir. Combined mutations (UL97 and UL54) may manifest high-level resistance to ganciclovir. Alternative therapies have been available in intravenous form only. These include foscarnet and cidofovir. Foscarnet is active against many ganciclovir-resistant strains of CMV, although associated with marked magnesium and potassium wasting, seizures (notably with calcineurin inhibitor therapy), and renal toxicity. Cidofovir may also be used, but often incurs significant nephrotoxicity and ocular toxicity. Viral polymerase UL54 mutations may cause resistance to foscarnet and cidofovir depending on the nature of the mutation. Multiple courses of antiviral therapy may be needed to cure resistant CMV infection. Given the toxicity of available medications, newer drugs are becoming available.

A new agent, letermovir, has demonstrated promise for the management of CMV infection in stem cell transplant recipients. Letermovir appears to have good oral bioavailability, and a low rate of adverse effects and drug–drug interactions.[96,97] Letermovir exerts its antiviral effect by interfering with the viral pUL56 gene product to disrupt the viral terminase complex.[98] The addition of hyperimmune globulin may be beneficial. Most centers try to reduce overall immunosuppression during therapy. Alternative agents include the dihydroorotate dehydrogenase inhibitors (leflunomide) approved for immunosuppression in treatment of rheumatologic diseases with useful, incidental activity against CMV (and possibly BK polyomavirus).[99–101] Effective use requires monitoring of drug levels and liver function tests. In phase III trials, maribavir, a competitive inhibitor of the pUL97 protein, appeared to be safe, but efficacy in CMV prevention was suboptimal.[102–104] CMX001 is a broad-spectrum oral lipid antiviral conjugate of cidofovir with activity against adenovirus as well as CMV; the drug has good bioavailability and some dose-limiting diarrhea.[105]

Epstein–Barr Virus

EBV is a ubiquitous herpesvirus that infects B lymphocytes. In immunosuppressed transplant recipients, primary EBV infection (and relapses in the absence of antiviral immunity) causes a mononucleosis-type syndrome, generally manifesting as a lymphocytosis (B cell) with or without lymphadenopathy or pharyngitis.[106–108] Meningitis, hepatitis, and pancreatitis also are observed. Remitting-relapsing EBV infection is common in children and may reflect the interplay between evolving antiviral immunity and immunosuppression.[109–111] Regardless of its mode of expression, this syndrome should suggest relative overimmunosuppression.

EBV also plays a central role in the pathogenesis of PTLD.[106,112] PTLD represents a spectrum of disease from benign B cell mononucleosis-like syndrome to monomorphic B cell lymphoma and tumors of T cell, natural killer cell, and null-cell origins (Fig. 31.3).[113,114] The most clearly defined risk factor for PTLD is primary EBV infection, which increases the risk for PTLD by 10- to 76-fold. PTLD may occur in the absence of EBV infection or in seropositive patients, and the role of EBV in the pathogenesis of non-B cell tumors is less clear.[45] Other risk factors include CMV coinfection, T cell depletion therapy, duration of immunosuppression, and, in adults, older age. Lymphomas constitute 15% of tumors among adult transplant recipients (51% in children) with mortality of 40% to 60%. Many deaths are associated with allograft failure after withdrawal of immunosuppression during treatment of malignancy.

Compared with the general population, PTLD has increased extranodal involvement, poor response to conventional therapies, and poor outcomes. The spectrum of disease is broad, as noted previously.[81] EBV-negative PTLD has been described, and T cell PTLD has been shown in allografts thought to have rejection or other viral infection. PTLD late (>1–2 years) after transplantation is more often EBV-negative in adults.[115]

The clinical presentations of EBV-associated PTLD vary widely and include:

- Unexplained fever (fever of unknown origin) with viremia
- A mononucleosis-type syndrome, with fever and malaise, with or without pharyngitis or tonsillitis (often diagnosed incidentally in tonsillectomy specimens); often no lymphadenopathy is observed
- Gastrointestinal bleeding, obstruction, or perforation
- Abdominal mass lesions
- Infiltrative disease of the allograft
- Hepatocellular or pancreatic dysfunction
- CNS mass lesions.

Diagnosis. Serologic testing is not useful for the diagnosis of acute EBV infection or PTLD in transplantation. Quantitative EBV viral load testing is required for the diagnosis and management of EBV-positive PTLD.[106,107,116] Serial assays are more useful in an individual patient than specific viral load measurements. Some data suggest that assays using unfractionated whole blood are preferable to plasma samples for EBV viral load surveillance. The diagnosis of PTLD may be suggested by the presence of a compatible clinical syndrome with demonstration of EBV viral load. WHO

standards now exist for EBV viral load assays; however, assays are not directly comparable between laboratories given laboratory-specific differences in performance.[117,118] Trends in individual patients over time using a single assay are most useful. The demonstration of EBV-specific nucleic acids in tissues may diagnose EBV-associated PTLD. RNA in situ hybridization against EBV-encoded small nuclear RNAs is more sensitive than the detection of viral DNA. The EBV-latent antigens EBNA-1, EBNA-2, and LMP-1 can be detected by immunohistochemistry.[119]

Management. Clinical management depends on the stage of disease. In the polyclonal form, particularly in children, reestablishment of immune function may suffice to cause PTLD to regress.[120] At this stage, it is possible that antiviral therapy might have some utility given the viremia and role of EBV, and of CMV, if present, as an immunosuppressive agent.[121] With progression of disease to extranodal and monoclonal malignant forms, reduction in immunosuppression may be useful, but alternative therapies are often required. In kidney transplantation, the failure to regress with significant reductions in immunosuppression may suggest the need to sacrifice the allograft for patient survival. Combinations of anti–B cell therapy (anti-CD20, rituximab), chemotherapy (CHOP: cyclophosphamide, hydroxydaunomycin, vincristine, prednisone), irradiation especially for CNS tumors, or adoptive immunotherapy with stimulated T cells have been used.[122–125]

Polyomaviruses

Polyomaviruses have been identified in transplant recipients in association with tubulointerstitial nephritis and nephropathy (PyVAN with BK virus [BKV], and JC virus [JCV]) and ureteric stenosis (BKV), and in association with demyelinating disease of the brain (JCV-associated progressive multifocal leukoencephalopathy [PML]). Less commonly, polyomaviruses have been identified in association with trichodysplasia spinulosa (TSV), in some malignancies (Merkel cell carcinoma [MCV]), and in condylomas. Tissue receptors for these human viruses are ubiquitous. The seroprevalence in adults for all polyomaviruses ranges from 40% to 90%. BKV resides in latency in renal tubular epithelial cells. JCV also has been isolated from renal tissues but has preferred tropism for neural tissues. Reactivation occurs with immunodeficiency and immunosuppression and tissue injury (e.g., ischemia-reperfusion).

BK Polyomavirus Infection. BKV is associated with a range of clinical syndromes in immunocompromised hosts, including viruria and viremia, ureteral ulceration and stenosis, and hemorrhagic cystitis.[126–130] Active infection of renal allografts has been associated with progressive loss of graft function (BKV nephropathy) in approximately 4% (range 1%–8%) of kidney transplant recipients; this is referred to as PyVAN (polyomavirus-associated nephropathy). BKV nephropathy is rarely recognized in recipients of extrarenal organs. The clinical presentation of disease is usually as asymptomatic, sterile pyuria, reflecting shedding of infected tubular and ureteric epithelial cells. These cells contain sheets of virus and are detected by urine cytology as "decoy cells." In some cases, the patient presents with diminished renal allograft function or with ureteric stenosis

and obstruction. In such patients, the etiologies of decreased renal function must be carefully evaluated (e.g., mechanical obstruction, drug toxicity, pyelonephritis, rejection, thrombosis, recurrent disease), and choices must be made between increasing immunosuppression to treat suspected graft rejection or reducing immunosuppression to allow the immune system to control infection.[131,132] Patients with BKV nephropathy treated with increased immunosuppression have a high incidence of graft loss. Reduced immunosuppression may stabilize renal allograft function but risks graft rejection. Other clinical syndromes may be associated with BKV, including pneumonitis, hemophagocytic syndrome, encephalitis, or PML.

Risk factors for BKV nephropathy include high-dose immunosuppression (particularly T cell depletion, tacrolimus, and mycophenolate mofetil), pulse-dose steroids for treatment of (presumed) graft rejection, ischemia-reperfusion injury, increased number of human leukocyte antigens (HLA) mismatches between donor and recipient, and the intensity of viremia in the pathogenesis of disease. Renal retransplantation for PyVAN is a risk factor for reinfection.[133,134] JCV may also cause nephropathy. The role of specific immunosuppressive agents has not been confirmed. The greatest incidence of BKV nephropathy is at centers with the most intensive immunosuppressive regimens.

Screening, Prevention, and Diagnosis. BKV infection is generally asymptomatic. Renal tubular cell injury in PyVAN is reflected in a rising serum creatinine. Most centers have developed screening programs to document early disease. The use of urine cytology to detect the presence of infected decoy cells in the urine has high sensitivity for BKV infection but a low (29%) predictive value for PyVAN. Detection of urine BKV by electron microscopy, urine BKV viral (DNA) loads greater than 7 log gEq/mL or BKV VP1 gene mRNA of >6 log copies/ng total urine RNA are useful diagnostically, keeping in mind that BKV molecular tests vary depending on the target and the matrix tested. Patients with BKV nephropathy tend to have higher plasma viral loads; in one study >7700 BKV copies per mL of plasma, $P < 0.001$, 50% positive predictive value, 100% negative predictive value compared with patients without disease.[135]

A high serum BKV viral load is considered a basis for reduction in immunosuppression, especially if serum creatinine has risen. The diagnosis should be made by the demonstration of BKV cytopathic changes with cellular infiltration consistent with the diagnosis of interstitial nephritis in the allograft and by immunohistology for BKV proteins, or by in situ hybridization for BKV nucleic acids in a renal biopsy. There is a semiquantitative scoring system for histologic changes of PyVAN.[135] For immunohistochemistry, cross-reacting antibodies against the large T antigen of the simian virus 40 or antibodies against BKVVP1 or agnoprotein have been used. PyVAN is characterized by intranuclear polyomavirus inclusion bodies in tubular epithelial and/or glomerular cells. Fibrosis is often prominent, occasionally with calcification. PyVAN is often focal, with false-negative biopsies in some cases. Graft rejection may accompany PyVAN, and complicates both diagnosis and management.

Recommendations regarding screening for BKV infection vary, but generally suggest testing once every 3 months during the first 2 years after transplantation, and at least

annually for years 2 to 5. A urinary test for BKV (cytology for decoy cells or urine BKV viral load over 7 log gEq/mL) is adequate for screening. Patients with high urinary BKV viral loads require testing for plasma BKV DNA. Screening can also be performed using plasma BKV DNA loads. For patients with plasma BKV DNA loads of >4 log10 gEq/mL on duplicate testing 2 to 3 weeks apart, a presumptive diagnosis of PyVAN should be made and immunosuppression reduced (see later). If screening is performed by plasma viral load, the interval between screening assays should be reduced to monthly for the first 6 months posttransplant. This reflects the faster onset of permanent renal injury in patients with circulating viremia compared with urinary excretion.

Treatment. There is no accepted treatment for PyVAN other than reduction in the intensity of immunosuppression. It is useful to monitor the response to such maneuvers using plasma viral load measurements.[135] Despite controversy, it is reasonable to reduce dosing of both calcineurin inhibitors and antimetabolites in a stepwise fashion while monitoring BKV plasma loads. Given the toxicity of calcineurin inhibitors for tubular cells, the role of renal tubular injury in the activation of BKV, and the need for anti-BKV T cell activity, these agents should be included in initial reductions. General targets include tacrolimus trough levels of <6 ng/mL, cyclosporine trough levels <150 ng/mL, sirolimus trough levels of <6 ng/mL, and/or mycophenolate mofetil daily dose equivalents of ≤1000 mg. Regardless of the approach, renal function (at least 1–2 times per week), drug levels, and viral loads (alternate weeks) must be monitored carefully during reductions. Rebiopsy may be needed for poor virologic and clinical responses.

The use of adjunctive antiviral therapies remains controversial. Some centers advocate the use of cidofovir, with or without probenecid, for BKV nephropathy in low doses (0.25–1 mg/kg every 2 weeks). Significant renal toxicity may be observed with cidofovir despite probenecid which may decrease efficacy. Leflunomide, an immunosuppressant used in rheumatoid arthritis, and fluoroquinolones have some anti-BKV activity in vitro, but little efficacy in vivo. Repletion of serum immunoglobulins may be considered.

Retransplantation has been successful in PyVAN patients with failed allografts, possibly as a reflection of immunity developing after reduction of immunosuppression. Some centers allow retransplantation after immunosuppression has been discontinued for some period (e.g., 6 months) and BKV is undetectable in blood and low in urine. Surgical removal of the allograft does not protect against future BKV infection or PyVAN but may be needed if immunosuppression cannot be reduced (double transplants, allosensitization) and/or elevated viral loads persist. In the future, measurements of BKV-specific cellular immunity after discontinuation of immunosuppression may help determine the optimal time for retransplantation.

JC Virus

Infection of the CNS by JC polyomavirus has been observed uncommonly in transplant recipients as PML (see Fig. 31.3). This infection may present with focal neurologic deficits or seizures and more slowly progressive neurologic lesions and may progress to death after extensive demyelination. PML may be confused with calcineurin neurotoxicity; both may respond to a reduction in drug levels. No proven therapies exist, although reduction of immunosuppression is commonly employed, an analogy to immune reconstitution in AIDS patients with PML.

Human Papillomavirus

Human papillomavirus (HPV) infection is associated with anogenital and skin precancers, cancers, and warts
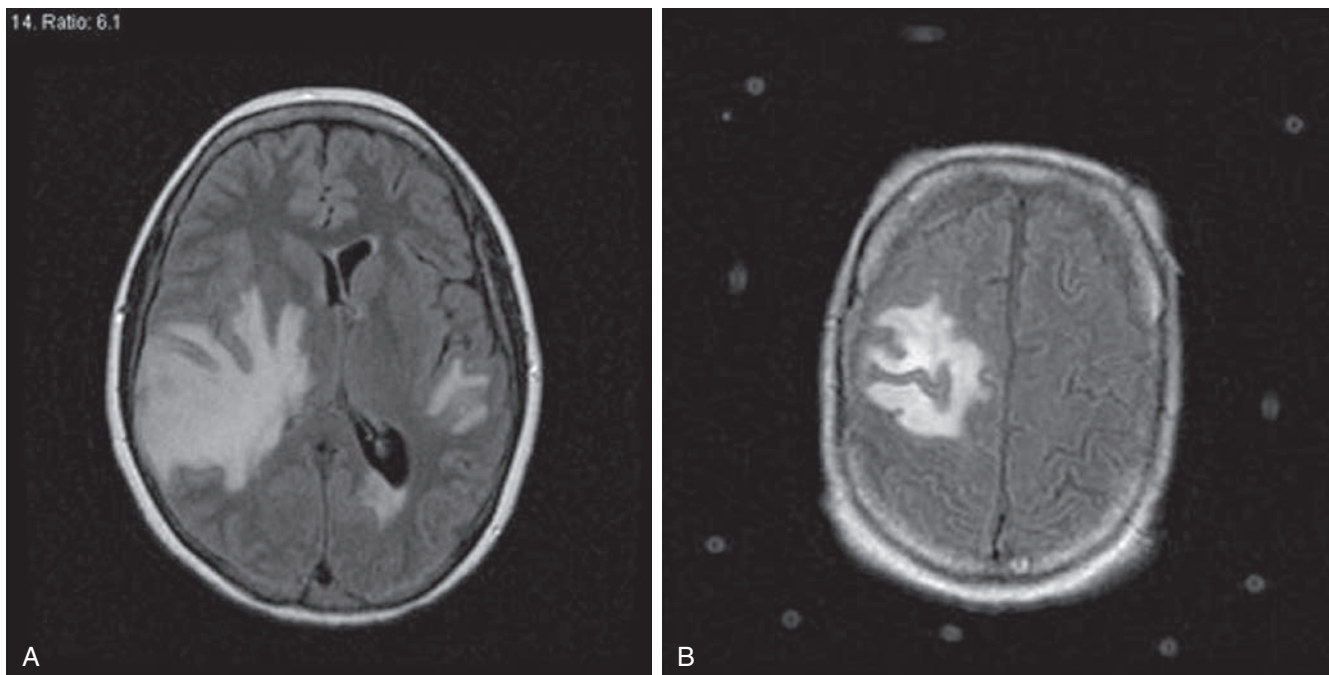

Fig. 31.3 (A) Central nervous system lymphoma with positive staining for Epstein–Barr virus (posttransplantation lymphoproliferative disorder) in a 63-year-old man 6 years postrenal transplantation. (B) Acute stroke syndrome in a 65-year-old man with progressive multifocal leukoencephalopathy.

associated with human HPV infections. Anogenital warts should be considered a marker for possible carriage of risk types for cervical and anal cancers including HPV16 and 18. Routine gynecologic and skin screening is mandatory for transplant recipients.

Human Immunodeficiency Virus

Successful organ transplantation in HIV-infected individuals (discussed earlier) has been achieved with effective antiretroviral therapies and full transplant immunosuppression including appropriate T cell depletion therapy. Rejection rates remain higher than in non-HIV-infected groups. Management requires careful tracking of immunosuppressive drug levels, avoidance of protease inhibitors in antiretroviral therapy (ART) selection if possible, and knowledge of HIV susceptibility patterns. Prophylaxis for opportunistic infections depends on the epidemiology of the individual (e.g., mycobacteria, *Coccidioides,* or *Histoplasma* exposures) and routine therapies. Donors with HIV or HCV infections are used at some centers with expertise in antiviral management in transplantation.

FUNGAL INFECTIONS

Transplant recipients are at risk for opportunistic infections with a variety of fungal pathogens, the most important of which are *Candida, Aspergillus,* and *Cryptococcus neoformans,* but also including the endemic mycoses.

Candida

The most common fungal pathogen in transplant patients is *Candida,* with more than 50% being non-*albicans* species.[136] Mucocutaneous candidal infection (e.g., oral thrush, esophageal infection, cutaneous infection at intertriginous sites, candidal vaginitis) is most common in diabetics, with high-dose steroid therapy, and during broad-spectrum antibacterial therapy. These infections are usually treatable through correction of the underlying metabolic abnormality and topical therapy with clotrimazole or nystatin (see Table 31.6C). Thrush also may complicate viral (HSV, CMV) or toxic (drugs including mycophenolate mofetil) esophagitis. Optimal management of *Candida* infection occurring in association with surgical drains or vascular access catheters requires removal of the foreign body and systemic antifungal therapy with fluconazole or echinocandin. A single positive blood culture result for *Candida* species necessitates systemic antifungal therapy; this finding carries a significant risk of dissemination in this population.

A special problem in kidney transplant recipients is candiduria, including in asymptomatic patients. Notably in individuals with poor bladder function, obstructing fungal balls can develop at the ureteropelvic junction, resulting in obstructive uropathy, ascending pyelonephritis, and the possibility of systemic dissemination.

Aspergillus

Invasive aspergillosis is a medical emergency in the transplant recipient, with the portal of entry being the lungs and sinuses in more than 90% of patients and the skin in most of the others. The predominant species depends on the clinical center and prior azole exposure.[137] The pathologic hallmark of invasive aspergillosis is blood vessel invasion, which accounts for the three clinical characteristics of this infection—tissue infarction, hemorrhage, and systemic dissemination with metastatic invasion. Soon after transplantation, CNS fungal infection is most often a result of *Aspergillus*; 1 year or later after transplantation, other fungi (Mucorales, dematiaceous fungi) become more prominent. The drug of choice for documented *Aspergillus* infection is voriconazole, despite its significant interactions with calcineurin inhibitors and rapamycin.[138,139] Isavuconazole, an azole antifungal with activity against yeasts, *Aspergillus,* and some Mucorales, has been shown to be safe and efficacious in solid-organ transplant recipients although it may require dose adjustment and therapeutic drug monitoring of immunosuppressive agents.[140–142] Liposomal amphotericin is an effective and fungicidal alternative, though a more toxic alternative in renal transplantation and should be reserved for cases in which azoles are contraindicated or not tolerated. Although not as toxic as amphotericin B preparations, echinocandins can be used in situations where azole and polyene antifungals are contraindicated, but they are not recommended as primary therapy for invasive aspergillosis, including renal infections. Combination therapy using voriconazole and anidulafungin has been studied in the hematologic malignancy population but did not show a survival advantage. Surgical debridement is sometimes required for successful clearance of such invasive infections.[138,139]

Central Nervous System Infections and Cryptococcus Neoformans

CNS infection in the transplant recipient may result from a broad spectrum of organisms.[2,143] Infections are often metastatic to the CNS from the blood and lungs. Viral etiologies include CMV (nodular angiitis), HSV meningoencephalitis, JCV (progressive multifocal leukoencephalopathy), and VZV. Locally epidemic pathogens (WNV, Eastern equine encephalitis) also must be considered. Bacterial pathogens can include *S. pneumoniae*, *Borrelia burgdorferi* (Lyme disease), *L. monocytogenes,* tuberculosis, *Nocardia,* and occasionally *Salmonella.* Brain and epidural abscesses have been observed and may be particularly problematic when secondary to an antibiotic-resistant pathogen. As noted earlier, fungi may be metastatic from lungs but also may spread from sinuses, skin, and the blood. Parasites with potential for CNS involvement include *Toxoplasma gondii* and *Strongyloides stercoralis.*

Given the spectrum of etiologies, precise diagnosis is essential (Table 31.8). A reasonable empirical regimen would treat pneumococcus and *Haemophilus influenzae* (ceftriaxone and vancomycin), *Listeria* (ampicillin), *Cryptococcus* (fluconazole or lipid formulation of amphotericin), and HSV (acyclovir) while awaiting data (lumbar puncture, blood cultures, and radiographic studies). Noninfectious etiologies, including calcineurin inhibitoOO)r toxicity, lymphoma, and metastatic cancer, should be included in the differential diagnosis. Molecular (HSV, VZV, *Toxoplasma*) and antigen (cryptococcal) assays on cerebrospinal fluid and biopsy (for noninfectious etiologies) may be needed for diagnosis.

Cryptococcus Neoformans. Cryptococcal infection is rarely seen in the transplant recipient until more than 6 months after transplantation. In the relatively intact transplant recipient, the most common presentation of

TABLE 31.8 Cerebrospinal Fluid Analysis in Transplantation

Opening pressure
Cell count with differential
Glucose and total protein concentrations
Gram stain and bacterial culture
India ink (or other fungal stain) and fungal culture
Viral culture (save sample if indicated)
Cryptococcal polysaccharide antigen
Fungal culture
Also consider: Histoplasma polysaccharide antigen (urine)
Also consider: Coccidioides immitis complement fixation antibodies (serum or CSF)

NUCLEIC ACID DETECTION (IN CLINICAL CONTEXT)

Herpes simplex virus 1 and 2
Varicella-zoster virus
Epstein–Barr virus
Cytomegalovirus
Human herpesvirus 6
JC virus
Enterovirus
Toxoplasma gondii (CSF or serum)

CYTOLOGY AND FLOW CYTOMETRY (CONSIDER FOR PTLD)

CSF, cerebrospinal fluid; PTLD, posttransplant lymphoproliferative disorder.

Fig. 31.4 *Cryptococcus neoformans* meningitis—India ink preparation of cerebrospinal fluid from a 53-year-old man, 16 months after renal transplantation, who presented with confusion and 7th nerve palsy without fever or meningismus.

cryptococcal infection is that of an asymptomatic pulmonary nodule with the organism present. In the "chronic ne'er-do-well" patient, pneumonia and meningitis are common, with skin involvement at sites of tissue injury (catheters) and prostate or bone involvement also reported.

Cryptococcosis should be suspected in transplant recipients who present more than 6 months after transplantation with unexplained headaches (especially when accompanied by fevers), decreased state of consciousness, failure to thrive, or unexplained focal skin disease (which requires biopsy for culture and pathologic evaluation).[144–146] Diagnosis is often achieved by serum cryptococcal antigen detection, but all such patients should have lumbar puncture for cell count, Gram stain, culture, India ink preparation, and cryptococcal antigen studies (Fig. 31.4). Initial treatment for CNS disease is liposomal amphotericin and 5-flucytosine (monitoring serum levels) followed by high-dose fluconazole. Extended courses of fluconazole suppression may be required for patients based on clinical progress or net degree of immunosuppression.[147,148] A gradual tapering of immunosuppression should also be considered with initiation of antifungal therapy, recognizing that IRIS, the clinical manifestations that mimic worsening cryptococcal disease, may occur in patients for whom reduction in immunosuppression has been too rapid.[149–151] This ultimately may require adjunctive use of corticosteroids as IRIS or scarring may cause obstruction, with increased cerebrospinal fluid pressure and hydrocephalus.

Strongyloides Stercoralis. With immunosuppressive therapy, *S. stercoralis* infection may activate more than 30 years after initial exposure. Such reactivation can result in either diarrheal illness or parasite migration with hyperinfection syndrome (characterized by hemorrhagic enterocolitis, hemorrhagic pneumonia, or both) or disseminated infection with accompanying (usually) gram-negative bacteremia or meningitis. Immigrants, refugees, travelers to and military personnel stationed in hyperendemic regions
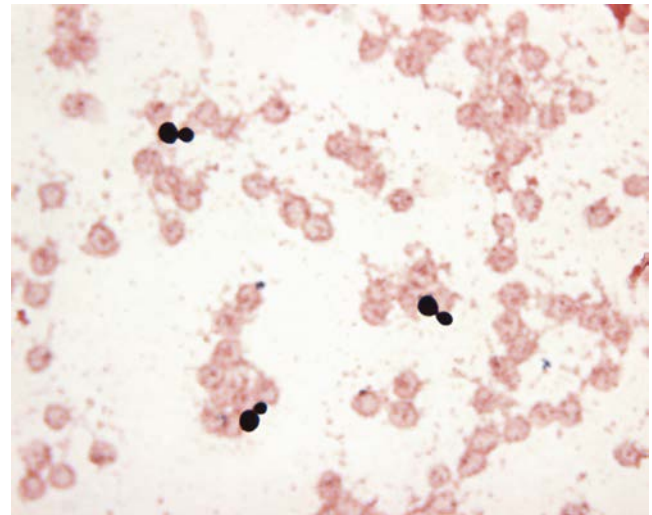
including Africa, Asia, Latin America, and the Caribbean should be screened with *Strongyloides* IgG serology before transplantation and should be treated with ivermectin preemptively if seropositive.

Pneumocystis and Fever With Pneumonitis

The spectrum of potential pulmonary pathogens in the transplant recipient is broad. Some general concepts are worth consideration. The depressed inflammatory response of the immunocompromised transplant patient may greatly modify or delay the appearance of a pulmonary lesion on radiograph. Focal or multifocal consolidation of acute onset is likely to be caused by bacteria. Similar multifocal lesions with subacute to chronic progression are more likely secondary to fungi, tuberculosis, or *Nocardia.* Large nodules are usually a sign of fungal or *Nocardia* infection. Subacute disease with diffuse abnormalities, either of the peribronchovascular type or miliary micronodules, are usually caused by viruses (especially CMV) or *Pneumocystis.* Additional clues can be found by examining pulmonary lesions for cavitation, which suggests necrotizing infection as may be caused by fungi (*Aspergillus* or Mucoraceae), *Nocardia, Staphylococcus,* and certain gram-negative bacilli, most commonly *Klebsiella pneumoniae* and *Pseudomonas aeruginosa.*

CT of the chest is useful when the chest radiograph is negative or when the radiographic findings are subtle or nonspecific. CT is also essential to determine the extent of the disease process, to discern the possibility of a simultaneous process (superinfection), and to select the optimal procedure for achieving a pathologic diagnosis.

Pneumocystis Pneumonia. The risk of infection with PJP is greatest in the first 6 months after transplantation (up to 10% without TMP-SMX or other prophylaxis) and during periods of increased immunosuppression.[152–155] There is a continued risk of infection in three overlapping groups of transplant recipients: (1) recipients who require higher

than normal levels of immunosuppression (notably corticosteroids) for prolonged periods because of poor allograft function or chronic rejection; (2) recipients with chronic CMV infection; and (3) recipients undergoing treatments (e.g., cancer chemotherapy, drug toxicity) that increase the level of immunodeficiency or neutropenia. The expected mortality secondary to PJP is increased in patients on cyclosporine compared with other immunocompromised hosts.

The hallmark of PJP is the presence of marked hypoxemia, dyspnea, and cough with a paucity of physical or radiologic findings. In the transplant recipient, PJP is generally acute to subacute in development. Atypical *Pneumocystis* infection (radiographically or clinically) may be seen in patients who have coexisting pulmonary infections or who develop disease while receiving prophylaxis with second-line agents (e.g., pentamidine or atovaquone). Patients presenting with PJP outside the usual highest risk period may have indolent disease that can be confused radiographically with heart failure. mTOR inhibitors (sirolimus and everolimus) have also been associated with the development of interstitial lung disease that can be confused radiographically and clinically with PJP.[156] Further, two case-control studies reported an association between the use of sirolimus and the development of PJP.[157,158] In such patients, invasive procedures are often required for definitive diagnosis.

Diagnosis, Therapy, and Prophylaxis. The characteristic hypoxemia of PJP produces a broad alveolar-arterial partial pressure of oxygen gradient. The level of serum lactate dehydrogenase is elevated in most patients with PJP (>300 IU/mL) although many other diffuse pulmonary processes also increase serum lactate dehydrogenase levels. No diagnostic pattern exists for PJP on routine chest radiograph. The chest radiograph may be entirely normal or reveal a classic pattern of perihilar and interstitial ground-glass infiltrates (see Fig. 31.1). Chest CT scans are more sensitive to the diffuse interstitial and nodular pattern than routine radiographs. The clinical and radiologic manifestations of PJP are virtually identical to the manifestations of CMV. The clinical challenge is to determine whether both pathogens are present; bronchoalveolar lavage may be helpful and the serum based $(1 \rightarrow 3)$-β-D-glucan test shows excellent sensitivity and very good specificity in the diagnosis of PJP.[159,160] Significant extrapulmonary disease is uncommon in the transplant recipient.

Early therapy with TMP-SMX is preferred; few kidney transplant patients tolerate full-dose TMP-SMX for prolonged periods.[154] This reflects the elevation of creatinine by trimethoprim (competing for secretion in the kidney), and the toxicity of sulfa agents for the renal allograft. Hydration and the gradual initiation of therapy may help. Alternative therapies are less desirable but have been used with success, including intravenous pentamidine, atovaquone, clindamycin with primaquine or pyrimethamine, and trimetrexate. The use of short courses of adjunctive steroids with a gradual taper is generally useful.

The importance of preventing *Pneumocystis* infection cannot be overemphasized. Low-dose TMP-SMX is well tolerated and should be used in the absence of concrete data showing true allergy or interstitial nephritis.[154,155] Alternative prophylactic strategies, including dapsone,

atovaquone, and inhaled or intravenous pentamidine, are less effective than TMP-SMX but are useful in patients with significant allergy to sulfa drugs. The advantages of TMP-SMX include increased efficacy; lower cost; availability of oral preparations; and possible protection against other organisms, including *T. gondii, Isospora belli, Cyclospora cayetanensis,* many *Nocardia* species, and common urinary, respiratory, and gastrointestinal bacterial pathogens. Alternative agents lack this spectrum of activity.

Urinary Tract Infection

Most urinary tract infections occur in the first year after kidney transplant.[161,162] A subset of patients experience recurrent disease and may suffer from pyelonephritis or bacteremia. Urinary tract infection beyond 6 months after transplantation is associated with reduced renal graft survival and increased mortality.[163] The risk of urinary tract infection after renal transplant is increased in women, with prolonged bladder catheterization, with increased intensity of immunosuppression, in recipients of deceased donor grafts, and, possibly, with vesicoureteral reflux. The risk for vesicoureteral reflux is dependent in part on the surgical approach to implantation of the ureter. The risk for candiduria is increased in patients who have received prior antimicrobial therapy, with neurogenic bladder, with indwelling urethral catheters, and in intensive care units. Most kidney transplant recipients with bacteriuria are asymptomatic, whereas pain with pyelonephritis represents transmural infection with local inflammation outside the denervated allograft causing what is perceived as allograft tenderness.

The major causative organisms include gram-negative bacilli (*Escherichia coli, Klebsiella, Pseudomonas, Enterobacter, Proteus*) and gram-positives (largely enterococci) and fungi (*Candida* species). Each of these groups may manifest important antimicrobial resistance; therapy should be based on susceptibility patterns and by the presence or absence of structural abnormalities (obstruction, delayed bladder emptying).[164] Thus cultures and imaging (ultrasound to exclude hydronephrosis) are required in patients with upper tract infection. Initial empiric therapy should include antimicrobial agents not used previously for prophylaxis and, where possible, not used in prior episodes of infection given the risk for antimicrobial resistance. Therapy can be narrowed based on susceptibility data. Short-course therapy is not used for treatment of uncomplicated urinary tract infection after transplantation; a 7-day minimum course with an effective agent is recommended. Upper tract disease (pyelonephritis) may require intravenous therapy initially and a 2- to 3-week total course. Clinical response should be documented. Asymptomatic candiduria should be treated in patients with renal allografts (although data are limited) with fluconazole (200 mg orally per day for 7–14 days). Upper tract disease with *Candida* species suggests obstruction and requires more intensive therapy (fluconazole 400 mg daily for 3–4 weeks). Echinocandins are not useful for treatment of most urinary tract infections because they achieve poor concentrations in the urine. Removal of stents and catheters is generally required for cure.

The prevention of urinary tract infections is altered by TMP-SMX prophylaxis. In the absence of instrumentation

or obstruction, TMP-SMX given for 6 months to 1 year post-transplant is generally effective. Few recent studies address whether the changing ecology of bacteria has reduced the efficacy of prophylaxis. In TMP-SMX intolerant patients, a fluoroquinolone may be used as prophylaxis with the addition of another agent against PJP.

Conclusions

Transplant infectious disease is increasingly characterized by the ability to monitor and prevent infection based on prophylaxis, new antimicrobial agents, and vaccination. Despite significant advances, infection poses a life-threatening challenge for many recipients. In the future, increased availability of pathogen-specific immune function tests, enhanced donor and recipient screening, and a better understanding of infection risks such as genetic polymorphisms should combine with advances in transplant immunosuppression to further reduce infection risks.

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