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INFECTION IN KIDNEY TRANSPLANT RECIPIENTS

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CHAPTER OUTLINE

OVERVIEW

RISK OF INFECTION

Epidemiological Exposures

- Donor-Derived Infections
- Recipient-Derived Exposures
- Community Exposures
- Nosocomial Exposures

Net State of Immunosuppression

TIMELINE OF INFECTION

First Phase (0–4 Weeks after Transplantation)

Second Phase (1–12 Months after Transplantation)

Third Phase (>6–12 Months after Transplantation)

ASSESSMENT OF INFECTIOUS DISEASES IN RECIPIENTS AND POTENTIAL DONORS BEFORE TRANSPLANTATION

Transplant Donor

- Deceased Donor Evaluation

Living Donor Evaluation

- Special Infectious Risks and Organ Procurement

Transplant Recipient

SELECTED INFECTIONS OF IMPORTANCE

General Considerations

Viral Pathogens

- Cytomegalovirus
- Epstein–Barr Virus
- Polyomaviruses
- JC Virus

Fungal Infections

- Candida
- Aspergillus
- Central Nervous System Infections and *Cryptococcus neoformans*
- Pneumocystis* and Fever with Pneumonitis
- Urinary Tract Infection

CONCLUSIONS

OVERVIEW

Successful management of infections in kidney transplant recipients is complicated by factors related to the immune status of the host and the epidemiology of infection.⁵⁷ 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 transplantation than in immunologically normal individuals. The interactions between infection, immunosuppression, and immune function play out in a complex environment in which multiple simultaneous processes, such as infection and graft rejection, may contribute to the clinical presentation. Immunocompromised patients tolerate invasive, established infection poorly with high morbidity and mortality, lending urgency to the need for an early, specific diagnosis to guide antimicrobial therapy. Given the T-lymphocyte dysfunction inherent to transplant immunosuppression, viral infections in particular are increased. These viral infections not only contribute to graft dysfunction, graft rejection, and systemic illness but also enhance the 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 epidemiological exposures of the patient, including the timing, intensity, and virulence of the organisms experienced.
2. The patient's "net state of immunosuppression," a conceptual measure of all the factors that contribute to the host's risk for infection.^{16,24}

The importance of any infectious exposure is determined by the ability of the host to "deal" effectively with the pathogen. Thus, the diabetic is at greater risk for bacterial skin infections than is a non-diabetic with calcineurin inhibitor therapy. An understanding of the risk factors for each transplant recipient allows the development of differential diagnoses for infectious syndromes, and the development of preventive strategies (prophylaxis, vaccination) appropriate to each individual's risk for infection.^{3,4}

Epidemiological Exposures

Epidemiologic exposures of importance 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

Infections derived from donor tissues and activated in the recipient are uncommon, but have been recognized as among the important infectious exposures in transplantation. Some of these infections are latent (e.g., viral, parasitic), whereas others are the result of active infection (e.g., sepsis) in the donor at the time

TABLE 31-1 Significant Epidemiological 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, West Nile)

Bacteria

Gram-positive and Gram-negative bacteria
(*Staphylococcus*, *Pseudomonas*, Enterobacteriaceae)
Mycobacteria (tuberculous and non-tuberculous)
Nocardia asteroides

Fungi

Candida species
Aspergillus
Endemic fungi (*Cryptococcus neoformans*)
Geographic fungi (*Histoplasma capsulatum*, *Coccidioides immitis*, *Blastomyces dermatitidis*)

Parasites

Toxoplasma gondii
Trypanosoma cruzi

Nosocomial Exposures*

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

Community Exposures*

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)
Geographic fungi and *Cryptococcus*, *Pneumocystis jiroveci*
Parasites (often distant) (*Strongyloides stercoralis*,
Leishmania, *Toxoplasma gondii*, *Trypanosoma cruzi*,
Naegleria fowleri)

*Colonization and infection of the recipient in advance of transplantation may occur due to these potential pathogens.

CMV, cytomegalovirus; 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.

of procurement. Common pathogens and endemic organisms causing significant morbidity in potential recipients form the basis of screening paradigms for organ donors.^{10,23,25,31,41}

Most types of infection have been recognized in transplant recipients at some point. Bacteremic or fungemic infections (e.g., *Staphylococcus aureus*, *Candida* species, Gram-negative bacteria) in donors at the time of donation can cause local (abscess) or systemic (bacteremic) infections, and may selectively adhere to anastomotic sites (vascular, urinary) to produce leaks or mycotic aneurysms. Some viral infections are ubiquitous, including cytomegalovirus (CMV) and Epstein-Barr virus (EBV), and are associated with particular syndromes and morbidity in the immunocompromised population (see section on selected infections of importance). The greatest risk of these infections is to seronegative (immunologically naïve) recipients who receive infected grafts from seropositive donors (latent viral infection). Some viruses demonstrate accelerated progression (lymphocytic choriomeningitis, lymphocytic choriomeningitis virus (LCMV), rabies) in transplant recipients. Latent infections, such as tuberculosis, toxoplasmosis, or strongyloidiasis, may activate from grafts many years after the initial, often unrecognized exposures.

Donor screening for transplantation is limited by the available technology and by the time available within which organs from deceased donors must be used.^{25,31} At present, routine evaluation of donors relies on antibody detection (serological) tests for common infections. As a result, some active infections remain undetected because seroconversion may not occur during acute infection. These limitations suggest that, to achieve the benefits of transplantation, some organs are implanted carrying unidentified pathogens. This risk is exhibited by clusters of donor-derived *Trypanosoma cruzi* (Chagas' disease), rabies virus, West Nile virus, and LCMV infections in organ transplant recipients. Molecular assays for donor screening (e.g., for human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV)) have the capacity to reduce the "window period" between exposure and development of a positive microbiological assay (nucleic acid test (NAT) instead of seroconversion) with some risk for false-positive assays given heightened NAT sensitivity.

Given the risk of transmission of infection from the organ donor to the recipient, certain infections 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. 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. Certain common infections are recognized during the evaluation of the transplant candidate, including HBV, HCV, and HIV. It is necessary to obtain a

TABLE 31-2 Common Infectious Exclusion Criteria for Organ Donors***Central Nervous System Infection**

Unknown infection of central nervous system (encephalitis, meningitis)
 Herpes simplex encephalitis or other encephalitis
 History of JC virus infection
 West Nile virus infection
 Cryptococcal infection of any site
 Rabies
 Creutzfeldt–Jakob disease
 Other fungal or viral encephalitis
 Untreated bacterial meningitis (requires proof of cure)

Disseminated and Untreated Infections

HIV (serological or molecular) (may be considered for HIV-positive recipient?)
 HSV (with active viremia), acute EBV (mononucleosis)
 Serological or molecular evidence of HTLV-I/HTLV-II
 Active hepatitis A (may consider non-viremic 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
 Untreated pneumonia
 Untreated bacterial or fungal sepsis (e.g., candidemia)
 Untreated syphilis
 Multisystem organ failure due to overwhelming sepsis, gangrenous bowel

*These must be considered in the context of the individual donor/recipient.

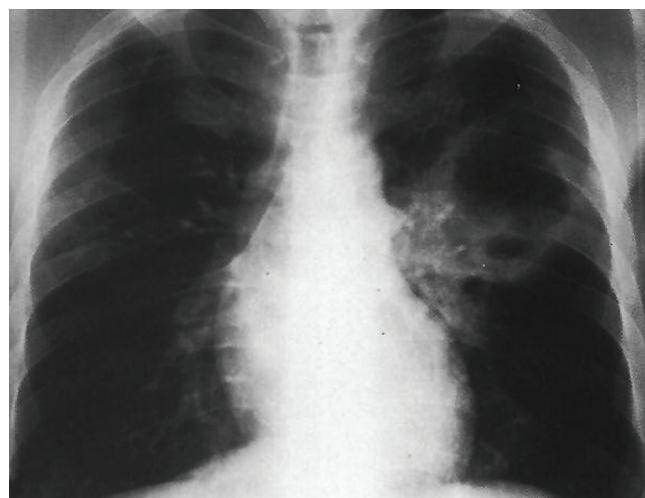
EBV, Epstein–Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; HTLV, human T-cell lymphotropic virus; SARS, severe acute respiratory syndrome.

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

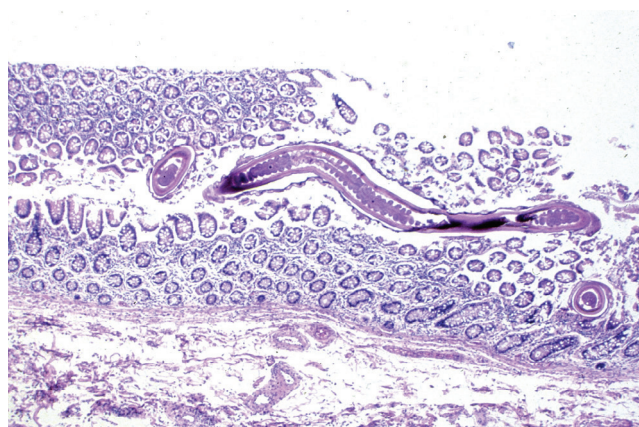
virus (VZV) or shingles), histoplasmosis, coccidioidomycosis, and paracoccidioidomycosis (Figure 31-1). Vaccination status should be evaluated (tetanus, HBV, childhood vaccines, influenza, pneumococcus); vaccines not previously administered should be considered in advance of transplantation as live virus vaccines are contraindicated after transplantation (Table 31-3). Dietary habits also should be considered, including the use of well water (*Cryptosporidium*), uncooked meats (*Salmonella*, *Listeria*), 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 risk for viral pneumonia and increased risk for bacterial or fungal superinfections. Community (contact or transfusion-associated) exposure to CMV and EBV may produce severe primary infection in the non-immune host. Recent and remote exposures to endemic, geographically restricted systemic mycoses (*Blastomyces dermatitidis*, *Coccidioides immitis*, and *Histoplasma capsulatum*) 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 due to immunosuppressive therapy (Figure 31-1). Such reactivation can result in either a diarrheal illness and parasite migration with hyperinfestation syndrome (characterized by hemorrhagic enterocolitis, hemorrhagic pneumonia, or both) or disseminated infection with accompanying (usually) Gram-negative bacteremia or meningitis. Gastroenteritis secondary to *Salmonella*, *Cryptosporidium*, and a variety



A



B

FIGURE 31-1 ■ Simultaneous *Pneumocystis* pneumonia and bacterial lung abscess secondary to co-infection 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 carinii* (*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*

Measles/mumps/rubella (MMR)
 Diphtheria/tetanus/pertussis (DTP)
 Poliovirus
Haemophilus influenzae b (Hib)
 Hepatitis B
Pneumococcus
 Influenza
 Varicella

*Live virus vaccinations are generally precluded in immunosuppressed hosts.

of enteric viruses can result in persistent infection, with more severe and prolonged diarrheal disease and an increased risk of primary or secondary blood stream invasion and metastatic infection.

Nosocomial Exposures

Nosocomial infections are of increasing importance. Organisms with significant antimicrobial resistance are present in most medical centers, including enterococci that are resistant to vancomycin, linezolid and/or quinupristin/dalfopristin, methicillin-resistant staphylococci, Gram-negative bacteria producing extended-spectrum beta-lactamases (ESBL), and fluconazole-resistant *Candida* species (Table 31-1). 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 jiroveci* between immunocompromised patients has been suggested by a number of case series.⁵² 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 prevent subsequent infections.

Net State of Immunosuppression

The net state of immunosuppression is a qualitative measure of the risk factors for infection in an individual, including immunosuppressive medications and iatrogenic conditions (Table 31-4). Among the most important are the following:

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)

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, hepatitis B and C, RSV)
 Graft rejection and treatment
 Cancer/cellular proliferation

CMV, cytomegalovirus; 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 so far
Plasmapheresis	Encapsulated bacteria
Costimulatory blockade	Unknown so far
Corticosteroids	Bacteria, <i>Pneumocystis jiroveci</i> , hepatitis B and C
Azathioprine	Neutropenia, papillomavirus (?)
Mycophenolate mofetil	Early bacterial infection, B cells, 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.

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 (Table 31-5).

TIMELINE OF INFECTION

With standardized immunosuppressive regimens, specific infections that occur most often vary in a predictable pattern depending on the time elapsed since transplantation (Figure 31-2). This is primarily a reflection of changing risk factors over time, including surgery and hospitalization, tapering of immunosuppression, acute and chronic

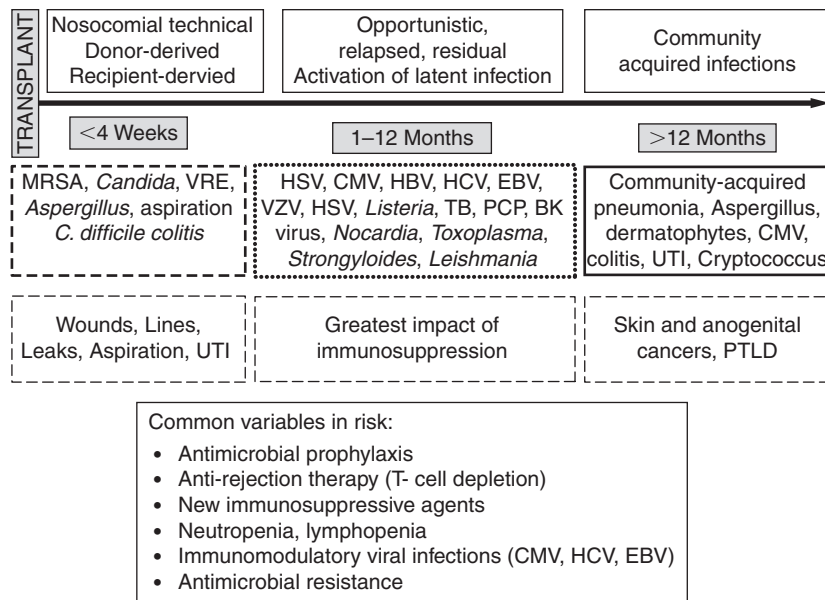


FIGURE 31-2 ■ The timeline of posttransplantation infections. Infection after transplantation tends to occur in a predictable pattern based on the epidemiologic exposure of the host and the nature of immune deficits. Patients with infections falling outside the usual patterns suggest unusual exposures or excessive immunosuppression. CMV, cytomegalovirus; EBV, Epstein–Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HSV, herpes simplex virus; MRSA, methicillin-resistant *Staphylococcus aureus*; PCP, *Pneumocystis jirovecii* pneumonia; PTLD, posttransplant lymphoproliferative disorder; TB, tuberculosis; UTI, urinary tract infection; VRE, vancomycin-resistant enterococcus; VZV, varicella-zoster virus.

rejection, and exposure to infections in the community.⁵⁷ The predicted pattern of infection changes with alterations in the immunosuppressive regimen (pulse-dose steroids or intensification for graft rejection), intercurrent viral infections, neutropenia (drug toxicity), graft dysfunction, or significant epidemiological 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 in HIV-infected and HCV-infected individuals, and broader epidemiological exposures from work or travel.

Figure 31-2 shows three overlapping periods of risk for infection after transplantation, each associated with differing patterns of common pathogens, as follows:

1. The perioperative period to approximately 4 weeks after transplantation, reflecting surgical and technical complications and nosocomial exposures
2. The period 1 to 6–12 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 excessive epidemiological hazard 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 of the routine preventive strategies from the Massachusetts General Hospital. Such strategies serve only to delay the onset of infection in the face of epidemiological pressure. The use of antimicrobial prophylaxis, vaccines, and behavioral modifications (e.g., routine hand washing or advice against digging in gardens without masks) may result only in a “shift to the right” of the infection timeline, unless the intensity of immunosuppression is reduced or immunity develops.

First Phase (0–4 Weeks after Transplantation)

During the first month after transplantation, three types of infection occur. The first type is infection or colonization present in the recipient before transplantation which 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*). All infection should be controlled or eradicated to the degree possible before transplantation.

The second type of early infection is donor-derived. This type may be nosocomially derived (resistant Gram-negative bacilli and *S. aureus* or *Candida* species) secondary to systemic infection in the donor (e.g., line infection)

TABLE 31-6 Renal Transplantation: Routine Antimicrobial Protocols

Pneumocystis jiroveci* Pneumonia (PCP) 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 posttransplantation. 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 PCP, 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.

G6PD, glucose-6-phosphate dehydrogenase; TMP-SMX, trimethoprim/sulfamethoxazole.

Cytomegalovirus and Antiviral Prophylaxis*

T-Cell Depletion (induction)?	Donor CMV Antibody	Recipient CMV Antibody	Prophylaxis*	Monitoring by CMV Viral Load or Antigenemia Assays
Yes	+	+	Valganciclovir po x 6 mos	After completion of prophylaxis based on intensity of immunosuppression. For symptoms, or monthly x 3 months from 6-9 mos
	-	+		
	+	-	Acyclovir, Famciclovir, or Valacyclovir (ACV/Fam/ValACV) x 6 mos	
	-	-		
No	+	+	Valganciclovir po x 3 mos	Monthly x 3 months from 3-6 mos
	-	+		
	+	-	ACV/Fam/ValACV x 3 mos	If clinically indicated
	-	-		
Intensified suppression for treatment of graft rejection	Either D+ or R+		Valganciclovir po x 2-3 mos	For symptoms or monthly x 3
	-	-	ACV/Fam/ValACV x 2-3 mos	

*First dose of ganciclovir is generally 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. CMV, cytomegalovirus. D+/R-, donor seropositive, recipient seronegative.

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.

or contamination during the organ procurement process. Rarely, infections transmitted from donor to recipient may emerge earlier than predicted (e.g., tuberculosis, histoplasmosis). Most recent clusters of donor-derived infection have been due to unfortunate timing – a donor who acquired acute infection (HIV, West Nile virus, rabies) prior to death due to unrelated causes.

The third and most common source of infection in the early period is related to the surgical procedure of transplantation. These infections include surgical wound infections, pneumonia (aspiration), bacteremia secondary to vascular access or surgical drainage catheters, urinary tract infections, and infections 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

non-immunosuppressed patients undergoing comparable surgery. Given immunosuppression, the signs of infection may be subtle, however, and the severity or duration usually is greater. Thus, bowel perforation may be clinically silent marked only by a rising white blood cell count 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) are the determinants of risk for these infections. Another common infection is *Clostridium difficile* colitis.

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 with additional coverage required for known risk factors (e.g., prior colonization with methicillin-resistant *S. aureus*).

For pancreas transplantation, additional perioperative prophylaxis against yeasts is common using fluconazole, mindful of potential increases in sirolimus and calcineurin inhibitor levels when used with azole antifungal agents.

Opportunistic infections are notable for their absence 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. It suggests that it is not the daily dose of immunosuppressive drugs that is important but rather the cumulative dose of these drugs – the “area under the curve” – that determines the true state of immunosuppression. The net state of immunosuppression is not great enough to support the occurrence of opportunistic infections, unless an exposure has been excessive. The occurrence of a single case of opportunistic infection in this period should trigger an epidemiological investigation for an environmental hazard.

Second Phase (1–12 Months after Transplantation)

The second phase of infection was originally 1–3 months, but has been altered by two main factors. These include: successful use of prophylaxis or monitoring programs against CMV and the herpesviruses, against *Pneumocystis* and urinary tract infections, and for HBV; and intensification of immunosuppression using more potent agents or antibody-based therapies with prolonged effects on immune function (Table 31-6). Infection in the transplant recipient 1–12 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., a urine leak, lymphocele, ureteric stricture, hematoma). Fluid collections in this setting generally require drainage.
2. Viral infections including CMV, HSV, shingles (VZV), human herpesvirus (HHV)-6 or HHV-7, EBV, hepatitis (HBV, HCV), and HIV. This group of viruses is unique. These infections are lifelong and tissue-associated, and are often transmitted with the allograft from seropositive donors. These viruses are systemically immunosuppressive, predisposing to opportunistic infection or acceleration of other infections (HCV) and predispose to graft rejection. The herpesviruses are prominent given the importance of T-cell function in antiviral control and the disproportionate degree of T-cell inhibition by most immunosuppressive regimens. Other common viral pathogens of this period include BK polyomavirus (in association with allograft dysfunction or polyomavirus-associated nephropathy (PVAN)) and community-acquired respiratory viruses (adenovirus, influenza, parainfluenza, respiratory syncytial virus, metapneumovirus). Superinfection of virally infected hosts is common.
3. Opportunistic infections secondary to *Pneumocystis jirovecii*, *Listeria monocytogenes*, *Toxoplasma gondii*, *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 average immunosuppression to maintain graft function or who has prolonged, untreated viral infections and other opportunistic infections, which predict long-term susceptibility to other infections (third phase, discussed below). Such patients may benefit from prolonged (lifelong) prophylaxis (antibacterial, antifungal, antiviral, or a combination) to prevent life-threatening infection.

The specific opportunistic infections that occur reflect the specific 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. During this period, anti-CMV strategies and trimethoprim/sulfamethoxazole prophylaxis are effective in decreasing the risk of infection. Trimethoprim/sulfamethoxazole prophylaxis effectively prevents *Pneumocystis* pneumonia and reduces the incidence of urinary tract infection and urosepsis, *Listeria monocytogenes* meningitis, *Nocardia* species infection, and *T. gondii*.

Third Phase (>6–12 Months after Transplantation)

Recipients who underwent transplantation more than 6–12 months previously can be divided into three groups in terms of infection 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 their major risk. Occasionally, such patients develop primary CMV infection (socially acquired) or infections related to underlying diseases (e.g., skin infections in diabetes). 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 as a result of 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. More recently, this has been the result of underlying disease progression (atherosclerosis, IgA or diabetes), calcineurin inhibitor toxicity, or humoral as well as cellular graft rejection. As a result, these patients are overimmunosuppressed relative to the risk for infection. These patients may benefit from lifetime maintenance trimethoprim/sulfamethoxazole prophylaxis and often fluconazole prophylaxis. In this group, one also should consider organisms more often associated with immune dysfunction of acquired immunodeficiency syndrome (AIDS) (*Bartonella*, *Rhodococcus*, *Cryptosporidium*, and microsporidia) and invasive fungal pathogens (*Aspergillus*, *Zygomycetes*, and Dematiaceae 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.^{3,13,31,34,38,43-45,71-73,78,79}

Transplant Donor

Deceased Donor Evaluation

A crucial feature in screening of deceased organ donors is time limitation. A useful organ must be procured and implanted before some microbiologic assessments have been completed. Major infections must be excluded, and appropriate cultures and samples must be obtained for future reference. As a result, bacteremia or fungemia may not be detected until after the transplantation has been performed. Such infections generally have not resulted in transmission of infection as long as the infection has been adequately treated in terms of use of antimicrobial agents to which the organism is susceptible and time. In recipients of tissues from 95 bacteremic donors, a mean of 3.8 days of effective therapy after transplantation seemed adequate to prevent transmission of susceptible pathogens. Longer courses of therapy in the recipient are preferred, targeting known donor-derived pathogens.^{17,26} 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 due to *Candida* species have resulted from contamination or candidemia at the time of procurement.^{57,58} These require susceptibility testing of the isolate and prolonged treatment (2–4 weeks) with effective agents to avoid pyelonephritis, abscess formation, mycotic aneurysm, or fungemia in the recipient. Vascular involvement by *Candida* species in the recipient requires at least 6 weeks of therapy. Certain acute infections (CMV, HSV, EBV, HIV, and HCV) may be undetected in the period before antibody formation. Viral nucleic acid detection assays are preferred for sensitivity. Likewise, the donor's clinical, social, and medical histories are essential to reducing the risk of such infections. In the presence of known infection, such infections must be treated before procurement if possible. Several more recent clusters of donor-derived infection have shown the risk for infection secondary to previously unrecognized pathogens, including lymphocytic choriomeningitis virus, Chagas' disease, and HSV, in addition to other, more common pathogens. Major exclusion criteria are outlined in Table 31-2.

Living Donor Evaluation

In contrast to the above-described scenario, the living donor procedure should be considered elective, and the evaluation should be completed and infections should be treated before such procedures. 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 (West Nile virus, severe acute respiratory syndrome (SARS), *Trypanosoma cruzi*). Live donors undergo a battery of serological 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 particular importance to the kidney transplant recipient is the exclusion of urinary tract infections (including yeasts) and bacteremia at the time of donation. Recent recommendations of the US Public Health Service suggest rescreening of potential donors within 7 days of donation using NAT for HIV, HCV, and HBV.

Special Infectious Risks and Organ Procurement

Tuberculosis. *Mycobacterium tuberculosis* from the donor represented approximately 4% of reported posttransplant tuberculosis cases in a review of 511 patients by Singh and Paterson.^{66,75} Much higher rates occur in endemic regions.⁵⁴ 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.²³ Factors favoring prophylaxis include a donor from an endemic region, use of a high-dose steroid regimen, or high-risk social environment.

TABLE 31-7 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
Cryptococcal polysaccharide antigen
<i>Histoplasma</i> polysaccharide antigen (if indicated)
<i>Coccidioides immitis</i> complement fixation antibodies (if indicated)
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
• <i>Toxoplasma gondii</i>
Cytology and flow cytometry

Parasites. Chagas' disease (*Trypanosoma cruzi*) has been transmitted by transplantation in endemic areas and more recently in the United States.^{10,17,48,74} Schistosomiasis and infection by *Strongyloides stercoralis* are generally recipient-derived issues. Though common, malaria and leishmaniasis have been rarely transmitted with allografts.

Viral Infections Other than Cytomegalovirus. EBV infection is a major risk factor for the development of PTLTD. The risk is greatest in the EBV-seronegative recipient of an EBV-seropositive allograft (i.e., donor seropositive, recipient seronegative (D⁺/R⁻)). This situation is most common in pediatric transplant recipients and in adults co-infected with CMV or receiving greater intensity of immunosuppression, notably with T-cell depletion and possibly with belatacept. Monitoring should be considered for at-risk individuals using a quantitative molecular assay (e.g., polymerase chain reaction) for EBV.^{2,28,29,47,56,66,81} EBV also is 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. HSV screening is performed by most centers despite the use of antiviral prophylaxis during the posttransplant period. VZV serological status is particularly important in 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).⁶¹ Other herpesviruses also may reactivate, with HHV-6 and HHV-7 serving as cofactors for CMV and fungal infections and, in endemic regions, Kaposi's sarcoma-associated herpesvirus (HHV-8) causing malignancy, notably in endemic regions in South America and surrounding the Mediterranean basin.

HBV surface antigen (HBsAg) and HBV core antibody (HBcAb) are used for screening purposes (see Chapter 32 for detailed discussion).^{1,43,49,71} 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 renal recipients; quantitative viral assays for HBV should be obtained to guide further therapy. The presence of HBsAg-negative, HBcAb-IgG-positive assays may be a false-positive result or reflect true, latent HBV infection.

HCV infection generally progresses more rapidly with immunosuppression and with CMV co-infection (see Chapter 32 for detailed discussion). HCV-seropositive kidney transplant candidates are more likely to develop cirrhosis and complications of liver failure. Therapies for HCV infection are limited, with the side effects of standard therapies (pegylated interferon- α and ribavirin) increased in the transplant population. Newer protease inhibitors and other agents are available and efficacy in the immunosuppressed host under investigation. Management involves monitoring disease progression by quantitative molecular viral assays for HCV RNA with

intermittent liver biopsy. Management is likely to change as newer HCV antiviral agents become available (see Chapter 32).

The use of HIV-infected donors for HIV-infected recipients is precluded in the United States but is under study in South Africa and elsewhere. The progression of untreated recipient HIV infection is rapid. Based on current criteria, donors may be excluded based on historical evidence of risk factors significant for HIV infection and confirmatory 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 is similar to HTLV-I serologically, 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 United States is now voluntary.^{29,35,55,76}

West Nile virus is a flavivirus associated with viral syndromes and meningoencephalitis and may be transmitted by blood transfusion and organ transplantation.^{7,36,46,59,72} 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.

Transplant Recipient

The pretransplant period is useful for obtaining travel, animal, environmental, and exposure histories; updating immunizations; and counseling of the recipient regarding travel, food, and other infection risks.¹⁵ Ongoing infection must be eradicated before transplantation. Two forms of infection pose a special risk – blood stream 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. Infected ascites or peritoneal dialysis fluid also must be cleared before surgery. 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 before transplantation (e.g., the initiation of immunosuppression to treat psoriasis or eczema). Finally, a history of more than one episode of diverticulitis should initiate an evaluation to determine whether sigmoid colectomy should be done before transplantation.

Among important considerations in transplant recipients are strongyloidiasis, tuberculosis, and AIDS. *Strongyloides* hyperinfestation syndrome (hemorrhagic enterocolitis, pneumonia, Gram-negative or mixed bacteremia, or meningitis) may emerge more than 30 years after transplantation. Empirical pretransplantation therapy of *Strongyloides*-seropositive recipients (ivermectin) prevents such infections.

The incidence of active tuberculous disease and the occurrence of disseminated infection secondary to *Mycobacterium tuberculosis* are higher in the transplant recipient than in the general population. Active tuberculous disease must be eradicated before transplantation. The major antituberculous drugs are potentially hepatotoxic, and significant drug interactions are common between antituberculosis agents and immunosuppressive agents. In patients with active infection, from endemic regions or with high-risk exposures, tuberculosis therapy should be initiated in all PPD-positive individuals before transplantation. Some judgment may be used as to the optimal timing of treatment in individuals without evidence of active or pleuropulmonary disease. 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 living exposures (e.g., in a shelter or other group housing).

For many patients receiving antiretroviral therapy, HIV infection has been converted from a progressively fatal disease to a chronic infection controlled by complex regimens of antiviral agents or highly active antiretroviral therapy (HAART). HAART has been associated with reduced viral loads, improved CD4⁺ lymphocyte counts, and reduced susceptibility to opportunistic infections. In the pre-HAART era, organ transplantation generally was associated with a rapid progression to AIDS. Prolonged disease-free survival with HAART has led, however, to a reconsideration of this policy. Kidney transplantation in HIV has been associated with good outcomes in individuals with controlled HIV infection and in the absence of HCV co-infection.^{8,12,20,59,70,68,80} Management requires experience with immunosuppressive agents and various HAART regimens. The main hurdle is the drug interactions between protease inhibitors and calcineurin inhibitors and the need for full immunosuppression despite HIV infection.

SELECTED INFECTIONS OF IMPORTANCE

General Considerations

The spectrum of infection in the immunocompromised host is quite broad. Given the toxicity of antimicrobial agents and the need for rapid interruption of infection, early, specific diagnosis is essential in this population. Advances in diagnostic modalities (e.g., CT or magnetic resonance imaging, molecular microbiologic techniques) may greatly assist in this process. The need for invasive diagnostic tools cannot be overemphasized, however. Given the diminished immune responses of the host, and the frequency of multiple simultaneous processes, invasive diagnosis is often required for specific microbiological diagnosis, to minimize side effects of therapy, and to improve clinical responses. The initial, empiric therapy is broad by necessity, with a rapid narrowing of the antimicrobial spectrum as data become available.

Among the decisions in anti-infective therapy is whether to reduce the intensity of immunosuppression, with the understanding that the risk of such an approach is graft rejection. For latent viral infections or tuberculosis, activation should be seen as evidence of excessive immunosuppression relative to the host's immune function. In contrast, for intercurrent bacterial or fungal infections, reductions in immunosuppression should be reconsidered 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). Co-infection with virus (CMV) is common and requires additional therapy. The adverse effects of reduced immune suppression during infection are best demonstrated in patients with cryptococcal meningitis in whom a "rebound" of inflammatory responses may result in worsening symptoms and hydrocephalus. This reflects the immune reconstitution and inflammatory syndrome (IRIS) seen with any patient in whom immune deficits are reversed in the face of ongoing inflammation.

Viral Pathogens

Cytomegalovirus

Invasive infection due to CMV has become less common due to the availability of effective antiviral therapies and diagnostic and monitoring assays for the virus (Table 31-6). However, even latent infection or low-level replication has important implications for transplant outcomes and strategies used to prevent (universal versus pre-emptive therapy with monitoring) and treat infection vary between centers. 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 syndrome with variable features of infectious mononucleosis, including hepatitis, nephritis, lymphadenitis, leukopenia, and/or thrombocytopenia
- Pneumonitis – often difficult to distinguish from apparently benign secretion
- Gastrointestinal invasion with esophagitis, colitis, gastritis, ulcers, bleeding, or perforation
- Hepatitis, pancreatitis, myocarditis, or chorioretinitis
- Meningoencephalitis
- Hemolytic uremic syndrome or microangiopathic thrombosis.

With the exception of chorioretinitis, the direct clinical manifestations of CMV infection usually occur 1–6 months after transplantation in the absence of prophylaxis. Viremia and symptomatic infections are rare during effective antiviral prophylaxis and have generally been delayed until after cessation of prophylaxis or develop in association with intensification of immunosuppression

(e.g., for rejection). Chorioretinitis occurs at low levels of viral replication and generally later in the posttransplant course.

The cellular and immunologic effects of CMV infection (discussed below) are the result of the suppression of a variety of host defense mechanisms and predispose to secondary invasion by *P. jiroveci*, *Candida*, and *Aspergillus* species, and other bacterial and fungal pathogens. 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 infection is in the setting of primary CMV infection when seronegative individuals receive grafts from latently infected, seropositive donors (D⁺R⁻), with subsequent reactivation of the virus with systemic dissemination. Over 50% of these patients become viremic in the absence of prophylaxis, often without symptoms. Many will become viremic after the cessation of antiviral, prophylaxis with symptomatic “late infection” occurring in up to a third of recipients previously treated with prophylaxis. Primary CMV infection may also occur in seronegative individuals after transfusion or sexual contacts in the community. This disease may be severe. The allograft may be a privileged site for viral replication because the major histocompatibility complex (MHC)-restricted, virus-specific, cytotoxic T cells have a decreased ability to eliminate virally infected cells in the presence of MHC mismatch between donor and recipient.

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 10–15% experience direct infectious disease syndromes in the absence of prophylaxis with a higher rate, up to 50%, following T-cell depletion therapies.

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

Pathogenesis of Infection. CMV activation occurs as the result of multiple factors, including the intensity of immunosuppression (notably pulsed-dose corticosteroids), the amount of virus in the graft, the use of lytic T-cell-depleting therapies, co-infections, notably 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- κ B. NF- κ B translocates to

the cell nucleus to activate the CMV major immediate-early promoter/enhancer and viral replication.

The risk for viral activation in the setting of intensified immunosuppression for graft rejection must be linked to prophylaxis, notably in the CMV serostatus D⁺/R⁻ combination. The alloimmune response carries both the effects of injury to the graft that is generally the site of greatest viral load and systemic inflammation. Thus, a bidirectional linkage exists between CMV replication and graft rejection. In an interesting study, Reinke et al.⁶⁷ showed that 17 of 21 patients for whom biopsy revealed evidence of “late acute rejection” demonstrated a response to antiviral therapy. Further, Lowance et al.⁵⁶ demonstrated that the prevention of CMV infection also resulted in a lower incidence of graft rejection.

The cellular and immunological effects of CMV (“indirect effects”) may be as important to the immunocompromised host as is invasive viral infection. The mechanisms for these effects are complex and relate to viral strategies to evade the host’s antiviral responses to allow human CMV-infected antigen-presenting cells to travel throughout the host to spread virus.

Diagnosis. Clinical management of CMV, including prevention and treatment, is based on an understanding of the causes of CMV activation and the available diagnostic techniques.²² CMV cultures generally are too slow and insensitive for clinical utility. A positive CMV culture (or shell vial culture) derived from respiratory secretions or urine is of little diagnostic value – many immunosuppressed patients secrete CMV in the absence of invasive disease. Serological tests are useful before transplantation to predict risk but are of little value after transplantation in defining clinical disease, including measurements of anti-CMV IgM levels, as seroconversion is generally delayed. Seroconversion to CMV provides evidence that the patient has developed some degree of immunity and appears to correlate with T-cell function as well as antibodies.

Quantitation of the intensity of CMV infection has been linked to the risk for infection in transplant recipients.^{6,8,14,32,40,41,49} Two types of quantitative assays have been developed: molecular and antigen detection assays.⁶ The antigenemia assay is a semiquantitative fluorescent assay in which circulating neutrophils are stained for CMV early antigen (pp65) that is taken up non-specifically as a measure of the total viral burden in the body. The molecular assays (direct DNA polymerase chain reaction, hybrid capture, amplification assays) are highly specific and sensitive for the detection of viremia.^{37,53} The most commonly used assays include plasma-based polymerase chain reaction testing and the whole-blood hybrid capture assay. Whole-blood and plasma-based assays cannot be directly compared and assays performed by different laboratories are often discordant. World Health Organization standards have been created to use in the harmonization of assays between centers. The highest viral loads often are associated with tissue-invasive disease, with the lowest in asymptomatic CMV infection. Viral loads in the CMV syndrome vary. Either assay can be used in management.

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

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

In these syndromes, the CMV assays are often negative. For the diagnosis of gastrointestinal CMV disease the demonstration of CMV inclusions in tissues and/or immunohistology for CMV antigens remains essential. The central role of assays is illustrated by the approach to the management of CMV risk (Table 31-6). 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 infection for 3–6 months. In the patient being treated for CMV infection, the assays provide an end-point for therapy and the initiation of prophylaxis.

Cytomegalovirus prevention. Prevention of CMV infection must be individualized for immunosuppressive regimens and the patient (Table 31-6).^{27,40,47,50,60,62,65} Two strategies are commonly used for CMV prevention – universal prophylaxis and pre-emptive therapy. Universal prophylaxis involves giving antiviral therapy to all at-risk patients beginning at or immediately after transplantation for a defined period. In pre-emptive therapy, quantitative assays are used to monitor patients at predefined intervals (generally weekly for weeks 1–12) to detect early disease. Positive assays result in therapy. Pre-emptive 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, opportunistic infection) also may be reduced by routine prophylaxis. In practice, neither universal prophylaxis nor pre-emptive 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 pre-emptive therapy for others. Infrequently, breakthrough disease and ganciclovir resistance have been observed with both approaches.¹

Given the risk for invasive infection, patients at risk for primary infection (CMV D⁺/R⁻) and seropositive patients receiving depleting anti-T-lymphocyte antibodies are generally given prophylaxis for 3–6 months after transplantation. Other groups are candidates for pre-emptive therapy if an appropriate monitoring system is in place, and patient compliance is good. Current data support the use of universal prophylaxis (not pre-emptive therapy), however, in the prevention of indirect effects of CMV infection, including PTLD, opportunistic infections, allograft rejection, and mortality.^{1,42} Increasingly, “late” disease has been observed after the completion of prophylaxis.^{38,39} Thus, monitoring may be useful after prophylaxis. The rate of late disease varies but is thought to be as high as 17–37% in D⁺/R⁻ recipients. This observation has

suggested the value of 6 months of prophylaxis in D⁺/R⁻ renal recipients (the IMPACT study).

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 valganciclovir (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. Prophylaxis should be reinitiated during treatments with antilymphocyte therapies. Given changing renal function after transplantation and the costs of medication, many regimens employ lower doses of valganciclovir. Such regimens should be coupled to monitoring to assure efficacy. After the completion of treatment for CMV disease (see below), many centers initiate a course of secondary prophylaxis (1–3 months). An alternative is a period of virologic monitoring for this period.

Treatment. The standard of care for treating invasive CMV disease is 2–4 weeks of intravenous ganciclovir (5 mg/kg twice daily, with dosage adjustments for renal dysfunction) until a quantitative assay for CMV is negative.^{40,47,62} In patients with mild to moderately severe symptoms, valganciclovir (900 mg po 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 3 months of CMV hyperimmune globulin in seronegative individuals (150 mg/kg/dose iv monthly) may be useful, but is 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 some with gastrointestinal disease treated with oral regimen. Repeat endoscopy should be considered to ensure the clearance of infection. In practice, it is reasonable to initiate therapy with intravenous ganciclovir, monitor weekly to assure a response, and treat until monitoring is negative. Such patients may benefit from 2–4 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.^{5,11,13} The risk for 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 10–14 days. Genetic resistance testing is useful in managing resistant CMV infection; mutations in the viral UL97 (thymidine kinase) or UL54 (DNA polymerase) genes can confer ganciclovir resistance.^{32,51} 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 are 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 some renal toxicity. Cidofovir may also be used, but often incurs significant nephrotoxicity and ocular toxicity. Liposomal cidofovir is under investigation. UL54 mutations may cause resistance to foscarnet and to 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, several investigational drugs are under study that may alter recommended therapies for antiviral-resistant CMV. Combination therapy (ganciclovir and foscarnet) may be useful, as is the addition of hyperimmune globulins. Most centers try to reduce overall immunosuppression during the course of therapy. Alternative agents include the dihydroorotate dehydrogenase inhibitors (leflunomide) approved for immunosuppression in treatment of rheumatological diseases with useful, incidental activity against CMV (and possibly BK polyomavirus).

Epstein–Barr Virus

EBV is a ubiquitous herpesvirus that infects B lymphocytes.^{2,29,30,66} 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.

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. Regardless of its mode of expression, this syndrome should suggest relative overimmunosuppression.

EBV also plays a central role in the pathogenesis of PTLD.^{14,47,55,53,59,70} PTLD represents a spectrum of disease from benign B-cell mononucleosis-like syndrome to monomorphic B-cell lymphoma as well as tumors of T-cell, natural killer cell, and null-cell origins (Figure 31-3). The most clearly defined risk factor for PTLD is primary EBV infection, which increases the risk for PTLD by 10–76-fold. PTLD may occur in the absence of EBV infection or in seropositive patients and the role of EBV in the pathogenesis of the non-B-cell tumors is less clear. Other risk factors include CMV co-infection, T-cell depletion therapy, duration of immunosuppression, and, in adults, older age. Posttransplant non-Hodgkin's lymphoma is a common complication of solid-organ transplantation. Lymphomas constitute 15% of tumors among adult transplant recipients (51% in children) with mortality of 40–60%. 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 and ranges from benign polyclonal, B-cell, infectious mononucleosis-like disease to malignant, monoclonal lymphoma.⁸⁰ Most disease is of B-cell origin, although T-cell, natural killer cell, and null cell tumors are described. EBV-negative PTLD has been

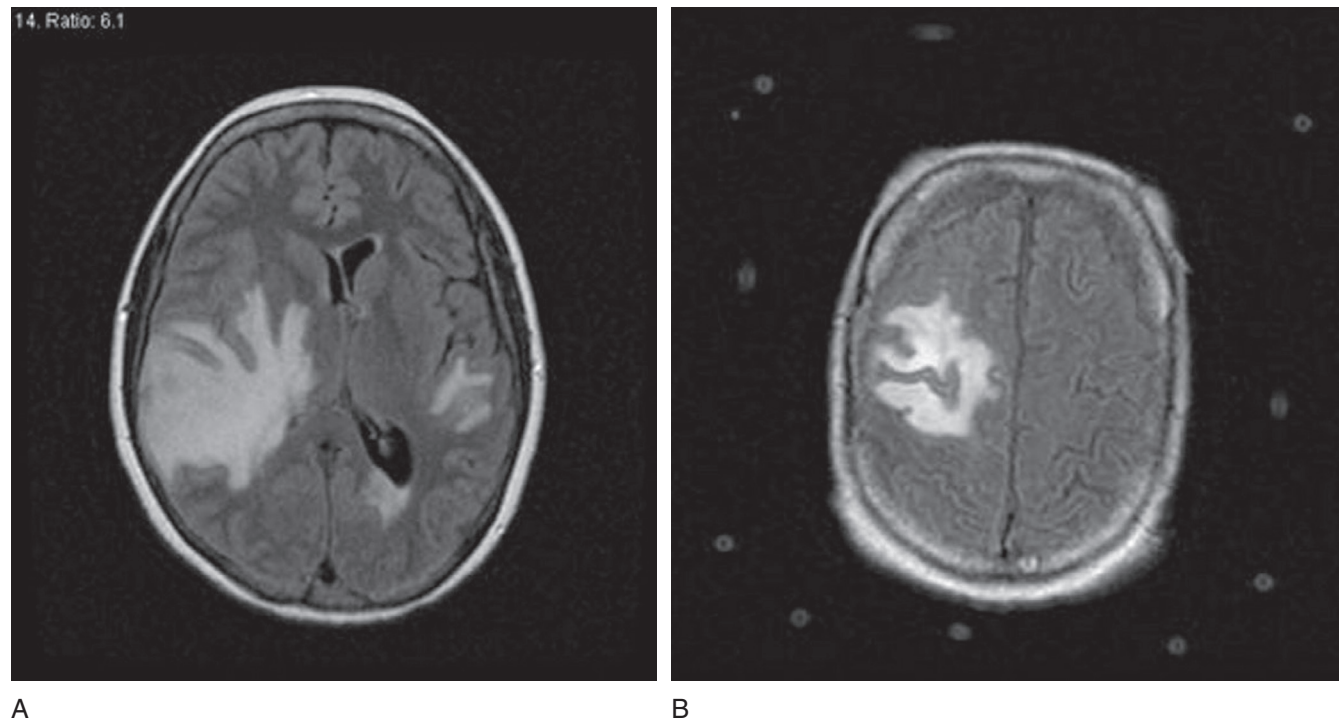


FIGURE 31-3 ■ (A) Central nervous system lymphoma with positive staining for Epstein–Barr virus (posttransplantation lymphoproliferative disorder) in a 63-year-old man 6 years status post renal transplantation. (B) Acute stroke syndrome in a 65-year-old man with progressive multifocal leukoencephalopathy.

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.

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
- Central nervous system (CNS) mass lesions.

Diagnosis. Serological 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 PTLD.^{2,5,20,28,29,66,72,74} Serial assays are more useful in an individual patient than specific viral load measurements. These assays are not standardized and cannot be directly compared between centers. 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. EBV viral load in whole blood and plasma appear to be similar but some controversy exists with respect to preferred sample type. Viral load monitoring is non-standardized and results may not be compared between clinical laboratories. 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.

Management. Clinical management depends on the stage of disease. In the polyclonal form, particularly in children, re-establishment of immune function may suffice to cause PTLD to regress. 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. With the 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.^{15,26,28,30}

Polyomaviruses

Polyomaviruses have been identified in transplant recipients in association with nephropathy and ureteral obstruction (BK virus), and in association with demyelinating disease of the brain (JC virus) similar to progressive multifocal leukoencephalopathy (PML) of AIDS. Adult levels of seroprevalence are 65–90%. BK virus resides in latency in renal tubular epithelial cells. JC virus also has been isolated from renal tissues but seems to have preferred tropism for neural tissues. Reactivation occurs with immunodeficiency and immunosuppression and tissue injury (e.g., ischemia-reperfusion).

BK Polyomavirus Infection. BK virus is associated with a range of clinical syndromes in immunocompromised hosts, including viruria and viremia, ureteral ulceration and stenosis, and hemorrhagic cystitis.^{22,34,40,42,58,60,61,63,77,80} Active infection of renal allografts has been associated with progressive loss of graft function (“BK nephropathy”) in approximately 4% (range 1–8%) of kidney transplant recipients; this is referred to as PVAN. BK nephropathy is rarely recognized in recipients of extrarenal organs. The clinical presentation of disease is usually as 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. Patients with BK nephropathy treated with increased immunosuppression have a high incidence of graft loss. Reduced immunosuppression may stabilize renal allograft function but risks graft rejection.

Risk factors for BK nephropathy are poorly defined. Some studies have implicated high-dose immunosuppression (particularly T-cell depletion, tacrolimus, and mycophenolate mofetil), pulse-dose steroids for treatment of graft rejection, ischemia-reperfusion injury, increased number of HLA mismatches between donor and recipient, and the intensity of viremia in the pathogenesis of disease. The role of specific immunosuppressive agents has not been confirmed. The greatest incidence of BK nephropathy is at centers with the most intensive immunosuppressive regimens.

Screening, Prevention, and Diagnosis. BK virus infection is generally asymptomatic. Renal tubular cell injury in PVAN 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 approximately 100% sensitivity for BK virus infection but a low (29%) predictive value.⁶⁴ Detection of urine BK virus by electron microscopy, urine BK viral (DNA) loads greater than 7 log gEq/mL or BK virus VP1 gene mRNA of >6 log copies/ng total urine RNA are useful diagnostically. Patients with BK nephropathy have

higher plasma viral loads (>7700 BK virus copies per mL of plasma, $P < 0.001$, 50% positive predictive value, 100% negative predictive value) when compared to patients without such disease.³⁴

A high serum BK viral load is considered a basis for reduction in immunosuppression, especially if serum creatinine has risen. However, the diagnosis should be made by demonstration of BK virus cytopathic changes with cellular infiltration consistent with the diagnosis of interstitial nephritis in the allograft and by immunohistochemistry for BK virus proteins, or by in situ hybridization for BK virus nucleic acids in a renal biopsy. There is a semiquantitative scoring system for histologic changes of PVAN. For immunohistochemistry, cross-reacting antibodies against the large T-antigen of the simian virus 40 or antibodies against BK virus VP1 or agnoprotein have been used. PVAN is characterized by intranuclear polyomavirus inclusion bodies in tubular epithelial and/or glomerular cells. Fibrosis is often prominent, occasionally with calcification. PVAN is often focal, with false-negative biopsies in some cases. Graft rejection may accompany PVAN, and complicates both diagnosis and management.

Recommendations regarding screening for BK virus infection vary, but generally suggest testing once every 3 months during the first 2 years after transplantation, and at least annually for years 2–5.^{33,34} A urinary test for BK virus (cytology for decoy cells or urine BK virus loads over 7 log gEq/mL) is adequate for screening. Patients with high urinary BK viral loads require testing for plasma BK virus DNA. Screening can also be performed using plasma BK virus DNA loads. For patients with plasma BK viral DNA loads of >4 log₁₀ gEq/mL on duplicate testing 2–3 weeks apart, a presumptive diagnosis of PVAN should be made and immunosuppression reduced (see below). 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 reduced time before permanent renal injury in patients with circulating viremia compared with urinary excretion.

Treatment. There is no accepted treatment for PVAN other than reduction in the intensity of immune suppression. It is useful to monitor the response to such maneuvers using plasma viral load measurements. Despite controversy, it is reasonable to reduce dosing of both calcineurin inhibitors and antimetabolites in a stepwise fashion while monitoring BK virus plasma loads. Given the toxicity of calcineurin inhibitors for tubular cells, the role of injury in the activation of BK virus, as well as the need for anti-BK 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 responses.

The use of adjunctive antiviral therapies remains controversial. Some centers advocate the use of cidofovir for BK nephropathy in low doses (0.25–1 mg/kg every

2 weeks). Significant renal toxicity may be observed with this agent. Leflunomide, an immunosuppressant used in rheumatoid arthritis, and fluoroquinolones have some anti-BK activity. Use of these agents should prompt consultation with clinicians expert in this area. Repletion of serum immunoglobulins and treatment with intravenous immunoglobulins have also been used with anecdotal success in some patients.

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

JC Virus

Infection of the CNS by JC polyomavirus has been observed uncommonly in transplant recipient as PML (Figure 31-3). This infection may present with focal neurologic deficits or seizures as well as more slowly progressive neurologic lesions and may progress to death following 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, on analogy to immune reconstitution in AIDS patients with PML.

Fungal Infections

In addition to the endemic mycoses, transplant recipients are at risk for opportunistic infections with a variety of fungal agents, the most important of which are *Candida*, *Aspergillus*, and *Cryptococcus neoformans*.

Candida

The most common fungal pathogen in transplant patients is *Candida*, with more than 50% being of non-*albicans* strains. 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 (Table 31-6). Thrush also may complicate viral (HSV, CMV) or toxic (drugs including mycophenolate mofetil) esophagitis. Optimal management of candidal infection occurring in association with the presence of vascular access catheters, surgical drains, and bladder catheters requires removal of the foreign body and systemic antifungal therapy with fluconazole or echinocandin.

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. A single positive culture result for *Candida* species from a blood specimen necessitates systemic antifungal therapy; this finding carries a significant risk of dissemination or invasion in this population.

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 those remaining. The predominant species depends on the clinical center and prior exposures to soil and construction sites. The pathological 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. Early in the course of transplantation, CNS involvement with fungal infection is most often due to *Aspergillus*; 1 year or later after transplantation, other fungi (*Zygomycetes*, dematiaceous fungi) become more prominent. The drug of choice for documented *Aspergillus* infection is voriconazole, despite its significant interactions with calcineurin inhibitors and rapamycin. Liposomal amphotericin is an equally effective alternative, and combination therapies are under study. Surgical debridement is usually essential for successful clearance of such invasive infections.

Central Nervous System Infections and *Cryptococcus neoformans*

CNS infection in the transplant recipient may result from a broad spectrum of organisms. Infections are often metastatic to the CNS from the blood stream and lungs. Viral etiologies include CMV (nodular angiitis), HSV meningoencephalitis, JC virus (progressive multifocal leukoencephalopathy), and VZV. Local epidemiology (West Nile virus, Eastern equine encephalitis) also must be considered. Common bacterial infections in addition to the pneumococcus include Lyme disease, *Listeria monocytogenes*, tuberculosis, *Nocardia*, and occasionally *Salmonella*. Brain abscess and epidural abscess have been observed and may be particularly problematic when secondary to methicillin-resistant *Staphylococcus aureus*, penicillin-resistant *Pneumococcus*, and quinolone-resistant streptococci. As noted earlier, fungi may be metastatic from lungs (*Aspergillus* and *Cryptococcus*) but also may spread from sinuses (Mucoraceae), skin (Dematiaceae), and the blood stream (*Histoplasma* and *Pseudallescheria/Scedosporium*, *Fusarium*). Parasites include *Toxoplasma gondii* and *Strongyloides stercoralis*.

Given the spectrum of etiologies, precise diagnosis is essential (Table 31-7). A reasonable empirical regimen would treat *Pneumococcus* and *Haemophilus influenzae* (ceftriaxone and vancomycin), *Listeria* (ampicillin), *Cryptococcus* (fluconazole or amphotericin), and HSV

(acyclovir) while awaiting data (lumbar puncture, blood cultures, and radiographic studies). Non-infectious etiologies, including calcineurin inhibitor toxicity, lymphoma, and metastatic cancer, should be included in the differential diagnosis. Molecular assays (HSV) and biopsy (for non-infectious 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 cryptococcal infection is that of an asymptomatic pulmonary nodule, often with active organisms present. In the “chronic ne’er-do-well” patient, pneumonia and meningitis are common, with skin involvement at sites of tissue injury (catheters) and in prostate or bone also reported.

Cryptococcosis should be suspected in transplant recipients who present 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 pathological evaluation) more than 6 months after transplantation. Diagnosis is often achieved by serum cryptococcal antigen detection, but all such patients should have lumbar puncture for cell counts, culture, India ink preparation, and cryptococcal antigen studies (Figure 31-4). Initial treatment is best with liposomal amphotericin and 5-flucytosine (monitoring serum levels) followed by high-dose fluconazole until the cryptococcal antigen is cleared from blood and cerebrospinal fluid. Lifetime prophylaxis is needed. IRIS may require adjunctive use of corticosteroids during the acute phase of CNS cryptococcal infection. IRIS or scarring may cause obstruction with increased cerebrospinal fluid pressure and hydrocephalus.

***Strongyloides stercoralis*.** *S. stercoralis* infection may activate over 30 years after initial exposure with immunosuppressive therapy. Such reactivation can result in either diarrheal illness or parasite migration with hyperinfection syndrome (characterized by hemorrhagic

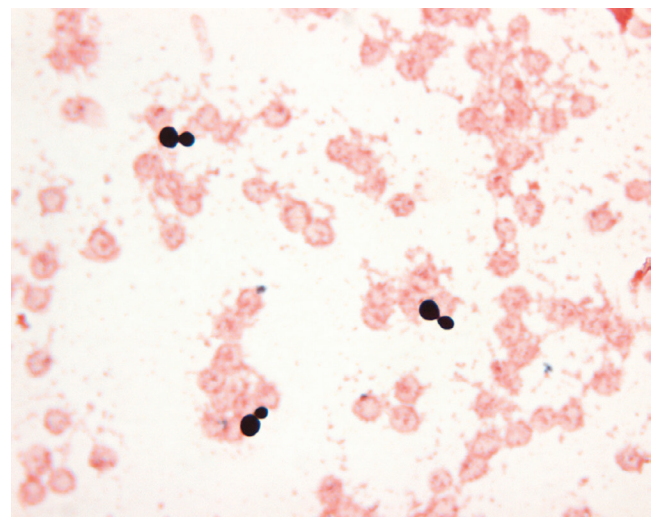


FIGURE 31-4 ■ *Cryptococcus neoformans* meningitis – India ink preparation of cerebrospinal fluid from a 53-year-old man 16 months after renal transplantation.

enterocolitis, hemorrhagic pneumonia, or both) or disseminated infection with accompanying (usually) Gram-negative bacteremia or meningitis. Patients from tropical areas and the southeastern United States should be screened with *Strongyloides* IgG serology prior to transplantation, and should be treated with ivermectin pre-emptively if seropositive.

Pneumocystis and Fever with Pneumonitis

The spectrum of potential pathogens of the lungs in the transplant recipient is broad. Some general concepts are worth consideration. As for all infections in transplantation, invasive diagnostic techniques are often necessary for specific microbiological diagnosis. This avoids unnecessary toxicities of antimicrobial agents and selection of optimal therapy. 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 bacterial infection. Similar multifocal lesions with subacute to chronic progression are more likely secondary to fungi, tuberculosis, or nocardial infections. Large nodules are usually a sign of fungal or nocardial infection, particularly if they are subacute to chronic in onset. Subacute disease with diffuse abnormalities, either of the peribronchovascular type or miliary micronodules, are usually caused by viruses (especially CMV) or *Pneumocystis*.^{54,75} 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*.^{35,76}

CT of the chest is useful when the chest radiograph is negative or when the radiographic findings are subtle or non-specific. CT also is essential to the definition of the extent of the disease process, to the discernment of the possibility of simultaneous processes (superinfection), and to the selection of the optimal invasive technique to achieve pathological diagnosis.

Pneumocystis Pneumonia. The risk of infection with *Pneumocystis jirovecii* pneumonia (PCP) is greatest in the first 6 months after transplantation and during periods of increased immunosuppression.^{18,19,52,54,57,75} In patients not receiving trimethoprim/sulfamethoxazole (or alternative drugs) as prophylaxis, most transplant centers report an incidence of *Pneumocystis* pneumonia of approximately 10% in the first 6 months after transplantation. There is a continued risk of infection in three overlapping groups of transplant recipients: (1) recipients who require higher than normal levels of immunosuppression for prolonged periods because of poor allograft function or chronic rejection; (2) recipients with chronic CMV infection; and (3) recipients undergoing treatments that increase the level of immunodeficiency, such as cancer chemotherapy or neutropenia secondary to drug toxicity. The expected mortality secondary to *Pneumocystis* pneumonia is increased in patients on cyclosporine compared with other immunocompromised hosts.

The hallmark of infection resulting from PCP is the presence of marked hypoxemia, dyspnea, and cough with a paucity of physical or radiological findings. In the transplant recipient, *Pneumocystis* pneumonia 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-choice agents (e.g., pentamidine or atovaquone). Patients outside the usual period of greatest risk for *P. carinii* (*jirovecii*) pneumonia may present with indolent disease, which may be radiographically confused with heart failure. In such patients, diagnosis often has to be made by invasive procedures. The role of rapamycin therapy in the clinical presentation is unknown. Numerous patients have been identified with interstitial pneumonitis while receiving rapamycin.^{3,9} This syndrome may occur in the presence or absence of concomitant infections (adenovirus, respiratory syncytial virus, *Pneumocystis*).

Diagnosis, Therapy, and Prophylaxis. The characteristic hypoxemia of *Pneumocystis* pneumonia produces a broad alveolar-arterial partial pressure of oxygen gradient. The level of serum lactate dehydrogenase is elevated in most patients with *Pneumocystis* pneumonia (>300 IU/mL). Many other diffuse pulmonary processes also increase serum lactate dehydrogenase levels, however. No diagnostic pattern exists for *Pneumocystis* pneumonia on routine chest radiograph. The chest radiograph may be entirely normal or develop the classic pattern of perihilar and interstitial ground-glass infiltrates (Figure 31-1). Chest CT scans are more sensitive to the diffuse interstitial and nodular pattern than routine radiographs. The clinical and radiological manifestations of *P. carinii* (*jirovecii*) pneumonia are virtually identical to the manifestations of CMV. The clinical challenge is to determine whether both pathogens are present. Significant extrapulmonary disease is uncommon in the transplant recipient. Bronchoalveolar lavage may be helpful.

Early therapy with trimethoprim/sulfamethoxazole is preferred; few kidney transplant patients tolerate full-dose trimethoprim/sulfamethoxazole for prolonged periods.^{21,52,69} 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. Although a reduction in the intensity of immunosuppression is generally considered a part of anti-infective therapy in transplantation, the use of short courses of adjunctive steroids with a gradual taper is generally useful.

The importance of preventing *Pneumocystis* infection cannot be overemphasized.^{19,52,68,69} Low-dose trimethoprim/sulfamethoxazole is well tolerated and should be used in the absence of concrete data showing true allergy or interstitial nephritis. Alternative prophylactic strategies, including dapsone, atovaquone, and inhaled or intravenous pentamidine, are less effective than trimethoprim/sulfamethoxazole but are useful in patients with significant allergy to sulfa drugs. Trimethoprim/sulfamethoxazole is the

most effective agent for prevention of infection caused by *P. carinii* (*jiroveci*). The advantages of trimethoprim/sulfamethoxazole include increased efficacy; lower cost; availability of oral preparations; and possible protection against other organisms, including *T. gondii*, *Isohora belli*, *Cyclospora cayentanensis*, *Nocardia asteroides*, and common urinary, respiratory, and gastrointestinal bacterial pathogens. Alternative agents lack this spectrum of activity.

Urinary Tract Infection

The majority of urinary tract infections occur in the first year after kidney transplantation. A subset of patients have recurrent disease and may suffer pyelonephritis or bacteremia. Urinary tract infection beyond 6 months after transplantation is associated with reduced renal graft survival and increased mortality. The risk of urinary tract infection after kidney transplantation 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 technical approach to implantation of the ureter taken in surgery. The risk for candiduria in particular 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, while 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*) as well as Gram-positives (largely enterococci) and fungi (*Candida* species). Each of these groups may manifest important antimicrobial resistance; therapy should be based on susceptibility pattern determinations. Therapy should be guided by the presence or absence of structural abnormalities (obstruction, delayed bladder emptying) as well as by the microbiology of infection. Thus, imaging (ultrasound to exclude hydronephrosis) as well as cultures should be obtained 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 development antimicrobial resistance. The spectrum of agents can be narrowed based on susceptibility data. Short-course therapy is not recommended for treatment of uncomplicated urinary tract infection after transplantation. The resolution of infection should be demonstrated (7-day minimum with effective agents) and upper tract disease (at least 2–3 weeks of therapy) and may require intravenous therapy initially. Asymptomatic candiduria should be treated in patients with renal allografts (although data are limited) with fluconazole (200mg orally per day for 7–14 days). Upper tract disease with *Candida* species should suggest obstruction and requires more intensive therapy (fluconazole 400mg daily for 3–4 weeks). The echinocandins are not useful for the treatment of most urinary tract infections as they achieve poor concentrations in the urinary tract. Removal of stents and catheters is generally required for resolution of urinary tract infection.

The prevention of urinary tract infections has been dramatically altered by the routine use of trimethoprim/sulfamethoxazole, which has the advantage of prevention of *Pneumocystis* pneumonia as well as urinary tract infections and other infections. Trimethoprim/sulfamethoxazole given for 6 months to 1 year post kidney transplantation is generally effective in the absence of instrumentation or obstruction. Few recent studies address whether the changing ecology of bacteria have reduced the efficacy of prophylaxis. In patients intolerant of trimethoprim/sulfamethoxazole, a fluoroquinolone may be used with the addition of another agent against PCP (atovaquone, dapstone).

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 screening of donors and recipients, and a better understanding of risk factors such as genetic polymorphisms should combine with advances in transplant immunosuppression to reduce risks of infection still further.

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