Chapter 29

Infection in Renal Transplant Recipients

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Successful management of infections in renal transplant recipients is complicated by factors related to immune function in the host and the epidemiology of infection in the immunocompromised host.[18] Transplant recipients are susceptible to a broad spectrum of infectious pathogens, manifest diminished signs and symptoms of invasive infection, and may develop systemic signs (e.g., fever) in response to noninfectious processes (e.g., graft rejection, drug toxicity) with multiple processes often present. 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 transplantation 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 renal 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
2. The patient's "net state of immunosuppression," which reflects a measure of all host factors contributing to the risk for infection

An understanding of these factors for each patient allows the development of differential diagnoses for infectious syndromes for transplant recipients and preventive strategies (prophylaxis, vaccination) appropriate to each individual's risk for infection.

Epidemiological Exposures

Exposures of importance can be divided into four overlapping categories—donor-derived infections, recipient-derived infections, community-derived exposures, and nosocomial exposures (Table 29-1).

Donor-Derived Infections

Infections derived from donor tissues and activated in the recipient are among the least appreciated and most important exposures in transplantation. Some of these infections are latent, whereas others are the result of the occurrence of active infection in the donor at the time of procurement. All known types of infections have been recognized in transplant recipients. Three types of infection merit special attention. First, bacteremic or fungemic infections (staphylococci, *Streptococcus pneumoniae, Candida*, *Salmonella, Escherichia coli*) in donors at the time of donation can selectively adhere to anastomotic sites (vascular, urinary) and may produce leaks or mycotic aneurysms. Second, some viral infections, including cytomegalovirus (CMV) and Epstein-Barr virus (EBV), 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 naive) recipients who receive infected grafts from seropositive donors (latent viral infection). Third, late, latent infections, such as tuberculosis, may activate many years after the initial exposure. Such infections may be difficult to treat when established because of interactions between the antimicrobial agents used to treat them (e.g., rifampin, streptomycin, isoniazid for mycobacteria) and the agents used in immunosuppressive therapy.

Donor screening for transplantation is limited by the available technology and by the time available within which organs from deceased donors must be used. 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 lymphocytic choriomeningitis virus infections in organ transplant recipients.

Table 29–1 Significant Epidemiological Exposures Relevant to Transplantation

Donor-Derived
Viral
Herpes group (CMV, EBV, HHV-6, HHV-7, HHV-8, HSV)
Hepatitis viruses (notably B and C)
Retroviruses (HIV, HTLV-I, HTLV-II)
Others
Bacteria
Gram-positive and gram-negative bacteria (*Staphylococcus, Pseudomonas*, Enterobacteriaceae)
Mycobacteria (tuberculous and nontuberculous)
Nocardia asteroides
Fungi
Candida
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 (also linezolid-resistant and quinupristin/dalfopristin-resistant enterococci)
Aspergillus
Non-*albicans Candida* strains
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 carinii (jiroveci)*
Parasites (often distant)
Strongyloides stercoralis
Leishmania
Toxoplasma gondii
Trypanosoma cruzi
Naegleria fowleri

CMV, cytomegalovirus; EBV, Epstein-Barr virus; HHV, human herpesvirus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; HTLV, human T cell lymphotropic virus; RSV, respiratory syncytial virus.

Table 29–2 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 Infection
HIV (serological or molecular)
HSV (with active viremia), acute EBV (mononucleosis)
Serological or molecular evidence of HTLV-I/HTLV-II
Active hepatitis A or hepatitis B
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; HIV, human immunodeficiency virus; HSV, herpes simplex virus; HTLV, human T cell lymphotropic virus; SARS, severe acute respiratory syndrome.

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 renal transplantation is typically elective surgery, it is reasonable to avoid donation from individuals with unexplained fever, rash, or infectious syndromes. Common criteria for exclusion of organ donors are listed in Table 29-2.

Recipient-Derived Exposures

Infections in the category of recipient-derived exposures reflect colonization or latent infections that reactivate in the setting of immunosuppression. It is necessary to obtain a careful history of 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, hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV). Vaccination status should be evaluated (tetanus, HBV, childhood vaccines, influenza, pneumococcus); if vaccines have not previously been given, they should be considered (Table 29-3). Dietary habits also should be considered, including the use of well water (*Cryptosporidium*), uncooked meats (*Salmonella, Listeria*), and unpasteurized dairy products (*Listeria*).

Table 29–3 Vaccinations to Consider before Transplantation

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

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, respiratory syncytial virus, and adenovirus) and by more atypical pathogens (HSV, VZV) carries risk for viral pneumonia and increased risk for bacterial or fungal superinfection. Community (contact or transfusion associated) exposure to CMV and EBV may produce severe primary infection in the nonimmune host. Recent and remote exposures to endemic, geographically restricted systemic mycoses (*Blastomyces dermatitidis, Coccidioides immitis*, 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 owing to the effects of immunosuppressive therapy (Fig. 29-1). 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, Campylobacter jejuni*, and a variety of enteric viruses can result in persistent infection, with more severe and prolonged diarrheal disease and an increased risk of primary or secondary bloodstream invasion and metastatic infection.

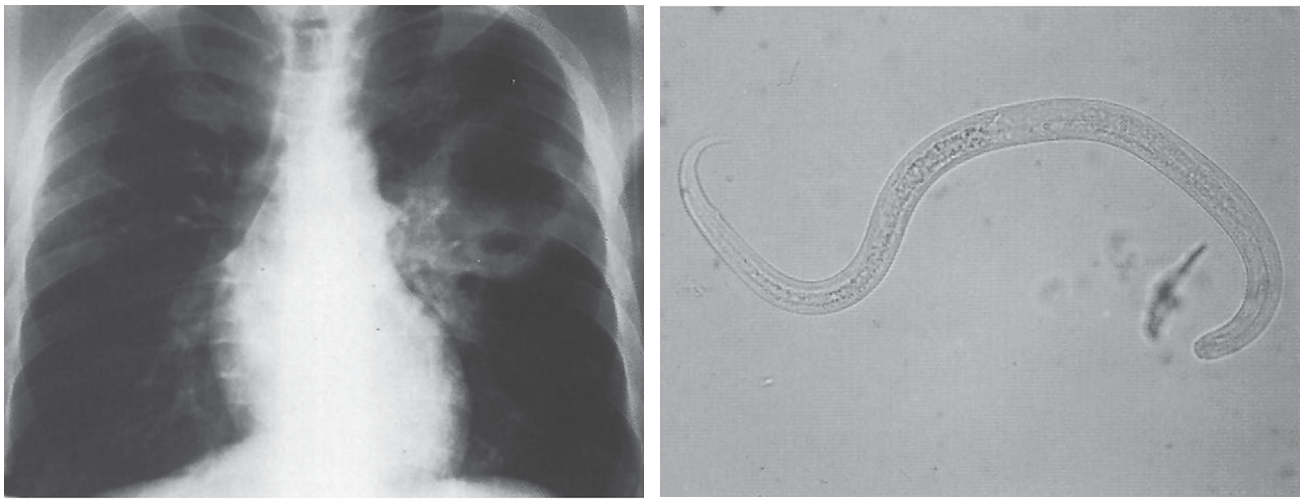
Nosocomial Exposures

Nosocomial infections are of increasing importance. Organisms with significant antimicrobial resistance are present in most medical centers, including vancomycin-resistant, linezolid-resistant, and quinupristin/dalfopristin-resistant enterococci; methicillin-resistant staphylococci, and fluconazole-resistant *Candida*. A single case of nosocomial *Aspergillus* infection in a compromised host 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. Each nosocomial infection should be investigated to ascertain the source and prevent subsequent infections. Nosocomial spread of *Pneumocystis carinii (jiroveci)* between immunocompromised patients has been suggested by a variety of case series. 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.

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 29-4). Among the most important are the following:

1. The specific immunosuppressive therapy, including number, dose, duration, and sequence of agents
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 surgical drainage catheterization
3. Prolonged instrumentation, including airway intubation and use of vascular access devices (e.g., dialysis catheters)
4. Prolonged use of broad-spectrum antibiotics
5. Renal or hepatic dysfunction, or both (in addition to graft dysfunction)



A B

Figure 29–1 Simultaneous *Pneumocystis* pneumonia and bacterial lung abscess secondary to coinfection by *Strongyloides stercoralis* in a Vietnamese kidney transplant recipient. **A,** Chest radiograph shows a lung abscess secondary to *Enterobacter* species. Bronchoscopic examination also revealed simultaneous *Pneumocystis carinii (jiroveci)* 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 29–4 Factors Contributing to the Net State of Immunosuppression

Immunosuppressive therapy—type, temporal sequence, intensity, cumulative dose
Prior therapies (chemotherapy or antimicrobials)
Mucocutaneous barrier integrity (catheters, lines, drains)
Neutropenia, lymphopenia (often drug induced)
Underlying immunodeficiency
Hypogammaglobulinemia from proteinuria
Complement deficiencies
Autoimmune diseases (systemic lupus erythematosus)
Other disease states (HIV, lymphoma/leukemia)
Metabolic conditions (uremia, malnutrition, diabetes, cirrhosis)
Viral infections (CMV, hepatitis B and C, RSV), which lead to immunosuppression
Graft rejection
Cancer/cellular proliferation

CMV, cytomegalovirus; HIV, human immunodeficiency; RSV, respiratory syncytial virus.

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 29-5).

TIMETABLE OF INFECTION

With standardized immunosuppressive regimens, specific infections that occur most often will vary in a predictable pattern depending on the time elapsed since transplantation (Fig. 29-2). This is primarily a reflection of the changing risk factors over time (surgery/hospitalization, immunosuppression, acute and chronic rejection, emergence of latent infections, and exposures to novel community infections).[18] The pattern of infections changes with alterations in the immunosuppressive regimen (pulse-dose steroids or intensification for graft rejection), intercurrent viral infection, neutropenia (drug toxicity), graft dysfunction, or significant epidemiological exposures (travel or food). The timeline remains a useful starting point, although 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 (e.g., travel).

Figure 29-2 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
2. The period 1 to 6 months after transplantation (depending on the rapidity of taper of immunosuppression and the use of antilymphocyte "induction" therapy), 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 29-6 outlines 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 antibiotic 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 to 4 Weeks after Transplantation)

During the first month after transplantation, three types of infection occur. The first type is infection present in the recipient before transplantation, which, after inadequate treatment, emerges in the setting of surgery, anesthesia, and immunosuppression. Pretransplantation pneumonia and vascular access infections are common examples of this type

Table 29–5 Immunosuppression and Infection

Antilymphocyte globulins (lytic) and alloimmune response	Activation of latent (herpes)virus, fever, cytokines
Plasmapheresis	Encapsulated bacteria
Costimulatory blockade	Unknown so far
Corticosteroids	Bacteria, *Pneumocystis (carinii) jiroveci*, hepatitis B and C
Azathioprine	Neutropenia, papillomavirus (?)
Mycophenolate mofetil	Early bacterial infection, B cells, late CMV (?)
Calcineurin inhibitors (cyclosporine/tacrolimus)	Enhanced viral replication (absence of immunity), gingival infection, intracellular pathogens
Rapamycin	Excess infections in combination with current agents, idiosyncratic pneumonitis syndrome

CMV, cytomegalovirus.

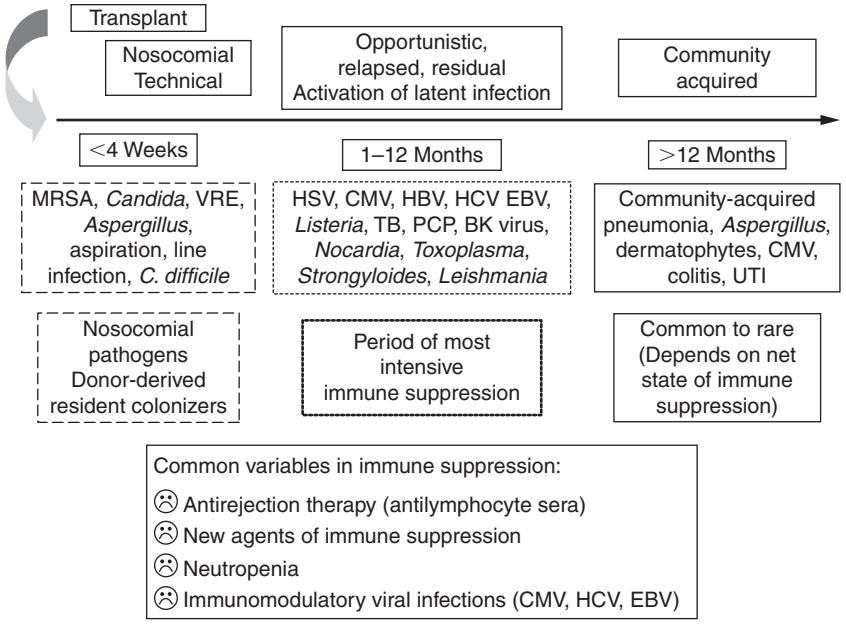


Figure 29–2 The timeline of infection after transplantation. CMV, cytomegalovirus; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HSV, herpes simplex virus; MRSA, methicillin-resistant *Staphylococcus aureus*; PCP, *Pneumocystis carinii (jiroveci)* pneumonia; TB, tuberculosis; UTI, urinary tract infection; VRE, vancomycin-resistant enterococcus.

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 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*) secondary to systemic infection in the donor (e.g., line infection) or contamination during the organ procurement process. The end result is a high risk of infection of vascular suture lines with mycotic aneurysm. Rarely, infections transmitted from donor to recipient may emerge earlier than predicted (e.g., tuberculosis, histoplasmosis).

The third and most common source of infection in the early period is related to the complex 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, are due to the same antimicrobial-resistant bacteria and *Candida* infections observed in nonimmunosuppressed patients undergoing comparable surgery. Given the immunosuppression, the signs of infection may be subtle, however, and the severity or duration usually is greater. 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 *C. difficile* colitis.

Limited perioperative antibiotic prophylaxis (i.e., from a single dose to 24 hours of an antibiotic such as cefazolin) is usually adequate with additional coverage only for known risk factors (e.g., prior colonization with methicillin-resistant *S. aureus*). For pancreas transplantation, 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 are at their highest during this time. The implications of this observation are 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"—in determining 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 to 6 Months after Transplantation)

Infection in the transplant recipient 1 to 6 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, 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 (often transmitted with the allograft

Table 29–6 **Renal Transplantation Routine Antimicrobial Protocols at Massachusetts General Hospital**

***Pneumocystis carinii (jiroveci)* Pneumonia 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 mo post-transplantation. Patients infected with CMV, with chronic rejection, or with recurrent infections are maintained on lifelong prophylaxis. A thrice-weekly regimen of TMP-SMX prevents *P. jiroveci* pneumonia, 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 wk; 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

CMV Prophylaxis

CMV Serological Status with or without ALT	Therapy*	Screening (Antigenemia)
$D^+/R^{-\dagger}$	Ganciclovir, 5 mg/kg intravenously for loading dose, then per renal function to discharge; then valganciclovir (in general, 450 mg/day for renal transplants) × 3 mo	Monthly for 6 mo after discontinuation of therapy‡
D^+ or R^+ with ALT	Ganciclovir, 5 mg/kg intravenously for first dose, then per renal function to discharge; valganciclovir daily × 6 mo	Monthly for 6 mo after discontinuation of therapy†
D^-/R^+ (no ALT)	Valganciclovir, 450 mg/day for renal transplants × 3 mo	Symptoms only
D^-/R^-	Famciclovir, 500 mg orally daily × 3-4 mo (or valacyclovir, 500 twice a day, or acyclovir, 400 three times a day); use of CMV-negative or leukocyte-reduced blood	Symptoms, fever/neutropenia
Status unknown with ALS	Ganciclovir, 5 mg/kg intravenously for first dose and daily (corrected for renal function) until serological status determined	

Fungal Prophylaxis

Mucocutaneous candidiasis can be prevented with oral clotrimazole or nystatin 2-3 times per day at times of steroid therapy or in the face of broad-spectrum antibacterial therapy and in diabetic transplant patients. Fluconazole, 200-400 mg/day for 10-14 days, is used to treat prophylaxis failures. Routine prophylaxis with fluconazole is used for pancreas transplants. Other prophylaxis must be determined based on risk for each institution and the presence or absence of colonization or other risk factors for fungal infection

*Drugs are not approved by the Food and Drug Administration at these doses. The doses of antiviral and antibacterial therapies generally *are not* reduced for neutropenia. Consider other options first.

†D^+/R^- = Donor seropositive, recipient seronegative.

‡ALT includes any of the lytic, lymphocyte-depleting antisera.

ALT, antilymphocyte therapy; CMV, cytomegalovirus; G6PD, glucose-6-phosphate dehydrogenase; TMP-SMX, trimethoprim/sulfamethoxazole.

from seropositive donors). More importantly, these viruses are systemically immunosuppressive 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 viral pathogens of this period include BK polyomavirus (in association with allograft dysfunction) and community-acquired respiratory viruses (adenovirus, influenza, parainfluenza, respiratory syncytial virus, metapneumovirus).

3. Opportunistic infection secondary to *P. carinii (jiroveci)*, *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 predicts long-term susceptibility to many other infections (third phase, discussed later). Such patients may require 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 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 *P. carinii (jiroveci)* pneumonia and reduces the incidence of urinary tract infection and urosepsis, *L. monocytogenes* meningitis, *Nocardia* infection, and *T. gondii*.

Third Phase (>6 to 12 Months after Transplantation)

Recipients who underwent tranplantation more than 6 months previously can be divided into three groups in

terms of infection risk. Most transplant recipients (70% to 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 in the absence of effective antiviral therapy (often reduction in immunosuppression) produces end-organ damage (e.g., BK polyomavirus leading to nephropathy, HCV leading to cryoglobulinemia or cirrhosis, CMV with chronic graft rejection) or malignancy (e.g., post-transplantation lymphoproliferative disease [PTLD] secondary to EBV, skin or anogenital cancer secondary to papillomaviruses).

A third group of patients has unsatisfactory allograft function and requires more intensive immunosuppressive therapy to preserve graft function. As a result, these patients appear overimmunosuppressed. These patients may have chronic viral infections and represent the "chronic ne'er-do-wells," who are at greatest risk for opportunistic infection. We give these patients 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 *Microsporida*) and invasive fungal pathogens (*Aspergillus, Zygomycetes*, and *Dematiaceae* or pigmented molds). Even minimal signs or symptoms warrant careful evaluation in this group of "high-risk" patients.

ASSESSMENT OF INFECTIOUS DISEASE IN RECIPIENT AND POTENTIAL DONOR BEFORE TRANSPLANTATION

Guidelines for pretransplant screening have been the subject of several more recent publications, including a consensus conference of the Immunocompromised Host Society, the American Society for Transplantation Clinical Practice Guidelines for the evaluation of renal transplant candidates, and the American Society of Transplant Surgeons (ASTS) Clinical Practice Guidelines for the evaluation of living renal transplant donors.[5,6,15,16,35,36,61,64,71]

Transplant Donor

Deceased Donor Evaluation

The crucial feature in screening of deceased 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.[22] Bacterial meningitis must be treated with antibiotics that penetrate the cerebrospinal fluid before organ procurement.

Certain acute infections (CMV, HSV, EBV, HIV, and HCV) may be undetected in the period before antibody formation. Viral DNA detection is preferred. 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 29-2.

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], *T. cruzi*). Live donors undergo a battery of serological tests (Table 29-7), purified protein derivative (PPD) skin test, and, if indicated, chest radiograph. The testing must be individualized based on unique risk factors (e.g., travel). Of particular importance to the renal transplant recipient is the exclusion of urinary tract infections (including yeasts) and bacteremia at the time of donation.

Special Considerations in Procurement

Mycobacterium tuberculosis from the donor represented approximately 4% of reported post-transplant tuberculosis cases in a review of 511 patients by Singh and Paterson.[66] 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.[4] Factors favoring prophylaxis include a donor from an endemic region, use of a high-dose steroid regimen, or high-risk social environment.

Chagas' disease (*T. cruzi*) has been transmitted by transplantation in endemic areas and more recently in the United States. Schistosomiasis and infection by *S. stercoralis* are generally recipient-derived problems.

Viral Infections Other than Cytomegalovirus

EBV infection is a major risk factor for development of PTLD. The risk is greatest in the EBV-seronegative recipient of an EBV-seropositive allograft (i.e., donor seropositive, recipient seronegative [D^+/R^-]). This situation is most common in pediatric transplant recipients and in adults coinfected with CMV or on higher levels of immunosuppression. Monitoring should be considered for at-risk individuals using a quantitative, molecular assay (e.g., polymerase chain reaction) for EBV.[26,53] EBV also is a cofactor for other lymphoid malignancies.

Table 29–7 Pretransplant Evaluation of Living Donors

Laboratory Test	All Patients	Patients with Exposure to Endemic Area	Quantitative Viral Studies Available (PCR)
Serologies			
CMV	√		√
HSV	√		√
VZV	√		
EBV	√		√
HIV	√		√
HBV: HBsAg	√		√
HBV: anti-HBs	√		
HCV	√		√
Treponema pallidum	√		
Toxoplasma gondii	√		
Strongyloides stercoralis		√	
Leishmania		√	
Trypanosoma cruzi		√	Blood smear
Histoplasma capsulatum		√	
Cryptococcus neoformans		√	Cryptococcal antigen
Coccidioides immitis		√	
Other Studies			
Urinalysis and culture	√		
Skin test: PPD	√		
Chest x-ray (routine)	√		
Stool ova and parasites (*Strongyloides*)		√	
Urine ova and parasites with or without cystoscopy		√ (for kidneys)	√ (schistosomiasis-endemic areas)

anti-HBs, antibody to hepatitis B surface antigen; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; PCR, polymerase chain reaction; PPD, purified protein derivative; VZV, varicella-zoster virus.

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 post-transplant 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). 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 malignancies.

HBV surface antigen (HBsAg) and HBV core antibody (HBcAb) are used for screening purposes (see Chapter 30 for detailed discussion). 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 may have viral DNA in the liver but may be appropriate as a donor for HBV-infected renal recipients; quantitative 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 coinfection (see Chapter 30 for detailed discussion). HCV-seropositive renal transplant candidates are more likely to develop cirrhosis and complications of liver failure. Therapies for HCV infection are currently limited, particularly in the transplant population; management is often conservative and involves monitoring disease progression by quantitative molecular viral assays with intermittent liver biopsy. Management is likely to change as newer HCV antiviral agents become available (see Chapter 30).

HIV-infected donors have rarely been used. The progression of recipient infection is rapid, and so far outweighs the benefits of transplantation. 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.[27,68]

West Nile virus is a flavivirus associated with viral syndromes and meningoencephalitis and may be transmitted by blood transfusion and organ transplantation.[69,70] 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.

SARS is a more recently described coronavirus, thought to be associated with exposure to civets or other animals common to the diet of certain regions of China. Tissue persistence is prolonged, and infection of transplant recipients

seems to be severe and often symptomatic. Organ procurement should exclude patients with recent acute illnesses meeting SARS criteria.

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. Ongoing infection must be eradicated before transplantation. Two forms of infection pose a special risk—bloodstream infection related to vascular access (including that for dialysis), and pneumonia, which puts the patient at high risk for subsequent lung infection with nosocomial organisms. Several other infections are commonly encountered and should be treated and cleared before transplantation. 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 one's 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, the 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 *M. 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, and transplantation was avoided in such individuals. Prolonged disease-free survival with HAART has led, however, to a reconsideration of this policy. Renal transplantation in HIV has been associated with good outcomes in individuals with controlled HIV infection and in the absence of HCV coinfection.[1,67a] Management requires experience with immunosuppressive agents and various HAART regimens.

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 the only method for optimal care. The initial therapy is broad by necessity, with a rapid narrowing of the antimicrobial spectrum as data become available.

The first choice of therapy is 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. In contrast, for intercurrent bacterial or fungal infections, reductions in immunosuppression might be reconsidered when evidence of resolution of infection is established. The selection of the specific reduction may depend on the organisms isolated. Similarly, reversal of some immune deficits (e.g., neutropenia, hypogammaglobulinemia) may be possible with adjunctive therapies (e.g., colony-stimulating factors or antibody). Coinfection with virus (CMV) is common and requires additional therapy.

Viral Pathogens

Cytomegalovirus

CMV is the most important pathogen in transplant recipients. It has a variety of direct and indirect effects.[18,60] The direct effects include the following:

- Fever and neutropenia syndrome with features of infectious mononucleosis, including hepatitis, nephritis, leukopenia, or thrombocytopenia
- Pneumonia
- Gastrointestinal invasion with colitis, gastritis, ulcers, bleeding, or perforation
- Hepatitis, pancreatitis
- Chorioretinitis

With the exception of chorioretinitis, the direct clinical manifestations of CMV infection usually occur 1 to 4 months after transplantation; chorioretinitis usually does not occur until later in the transplant course.

Although CMV is a common cause of clinical infectious disease syndromes, the *indirect effects* of viral infection are equally important. CMV infection produces a profound

suppression of a variety of host defenses, predisposing to secondary invasion by such pathogens as *P. carinii (jiroveci), Candida*, *Aspergillus*, and some bacteria. CMV also contributes to the risk for graft rejection, PTLD, HHV-6 and HHV-7 infections, and acceleration of HCV infection. The mechanisms for these effects are complex, including alteration of T cell number and function and major histocompatibility complex (MHC) synthesis, and the elaboration of an array of proinflammatory cytokines, chemokines, and growth factors.

PATTERNS OF TRANSMISSION

Transmission of CMV in the transplant recipient occurs in one of three patterns—primary infection, reactivation, and superinfection.[18]

Primary Cytomegalovirus Infection. Primary infection occurs most often when seronegative individuals receive grafts from latently infected, seropositive donors (D^+/R^-), with subsequent reactivation of the virus and systemic dissemination after transplantation. Forty percent to 50% of these patients experience direct infectious disease manifestations of CMV, whereas most are viremic, often without symptoms. Primary CMV infection also may occur in seronegative individuals after transfusion or exposure in the community. This disease may be severe.

Reactivation Cytomegalovirus Infection. In reactivation infection, seropositive individuals reactivate endogenous virus after transplantation ($D^{+/-}/R^+$). When conventional immunosuppressive therapy is used (e.g., no antilymphocyte antibody treatment), approximately 10% to 15% experience direct infectious disease syndromes, with a higher rate with the use of induction antilymphocyte therapy. Fifty percent of these individuals are viremic, often without symptoms.

Cytomegalovirus Superinfection. Virus may be reactivated in the setting of an allograft from a seropositive donor transplanted into a seropositive recipient (D^+/R^+).

PATHOGENESIS

Control of CMV infection is via MHC-restricted, virus-specific, cytotoxic T lymphocyte response ($CD8^+$ cells) controlled by $CD4^+$ lymphocytes. Seroconversion is a marker for the development of host immunity. The major effector for (re)activation of virus is the nature of the immunosuppressive therapy administered. Depleting–antithymocyte polyclonal and monoclonal antibodies are direct activators of viral infection (mimicking the alloimmune response) and provoke the elaboration of tumor necrosis factor-α and the other proinflammatory cytokines that enhance viral replication. Cyclosporine, tacrolimus, rapamycin, and prednisone (other than pulse doses) have limited ability to reactivate latent CMV, whereas azathioprine, mycophenolate mofetil, and cyclophosphamide are moderately potent in terms of promoting viral reactivation. These agents also perpetuate infection after it is established.

Allograft rejection is a major stimulus for CMV activation and vice versa. The CMV infection has been linked to a diminished outcome of renal and other allografts. Reinke and colleagues[60] showed that 17 of 21 patients for whom biopsy specimens revealed evidence of "late acute rejection" showed a response to antiviral therapy. Multiple studies have shown that the prevention of CMV infection also resulted in a lower incidence of graft rejection.[41]

DIAGNOSIS

Clinical management of CMV, including prevention and treatment, is important for the transplant recipient. It is based on an understanding of the causes of CMV activation and the available diagnostic techniques. 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 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 (this statement includes measurements of anti-CMV IgM levels). Should a patient seroconvert to CMV, this is evidence that the patient has been exposed to CMV and has developed some degree of immunity. Seroconversion in transplantation is generally delayed, however, and not useful for clinical diagnosis. The demonstration of CMV inclusions in tissues in the setting of a compatible clinical presentation is the "gold standard" for diagnosis.

Quantitation of the intensity of CMV infection has been linked to the risk for infection in transplant recipients.[7,33,42,50,65] Two types of quantitative assays have been developed—molecular and antigen detection assays. The antigenemia assay is a semiquantitative fluorescent assay in which circulating neutrophils are stained for CMV early antigen (pp65) that is taken up nonspecifically 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. 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. 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 noninvasive diagnosis in many patients with two important exceptions:

- Neurological disease, including chorioretinitis
- Gastrointestinal disease, including invasive colitis and gastritis

In these syndromes, the CMV assays are often negative, and invasive diagnosis (biopsy) may be needed.

The central role of assays is illustrated by the approach to management of CMV risk (see Table 29-6). 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 to 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. Two strategies are commonly used for CMV prevention—universal prophylaxis and preemptive therapy. Universal prophylaxis involves giving antiviral therapy to all at-risk patients beginning at or immediately after transplantation for a defined period. In preemptive therapy, quantitative assays are used to

monitor patients at predefined intervals to detect early disease. Positive assays result in therapy. Preemptive therapy incurs extra costs for monitoring and coordination of outpatient care, while reducing the cost of drugs and the inherent toxicities. Prophylaxis has the possible advantage of preventing not only 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 preemptive therapy is perfect. Infrequently, breakthrough disease and ganciclovir resistance have been observed with both approaches.[34]

Given the risk for invasive infection, patients at risk for primary infection (CMV D^+/R^-) are generally given prophylaxis for 3 to 6 months after transplantation. We use 6 months of prophylaxis in patients receiving depleting anti–T lymphocyte antibodies. Other groups are candidates for preemptive therapy *if* an appropriate monitoring system is in place, and patient compliance is good. Current data support the use of universal prophylaxis (not preemptive therapy), however, in the prevention of indirect effects of CMV infection, including PTLD, opportunistic infections, allograft rejection, and mortality.[34]

TREATMENT

The standard of care for treating invasive CMV disease is at least 2 to 3 weeks of intravenous ganciclovir (5 mg/kg twice daily, with dosage adjustments for renal dysfunction) until a quantitative assay for CMV is negative. In patients slow to respond to therapy and who are seronegative, the addition of 3 months of CMV hyperimmune globulin (150 mg/kg/dose intravenously given every 3 to 4 weeks) may be useful. Relapses occur, primarily in patients not treated beyond the achievement of a negative quantitative assay. The use of completely oral regimens for treatment appears to be effective with the exception of invasive gastrointestinal disease. We treat intravenously until there is evidence of a good response and then switch to oral treatment or oral treatment with close monitoring of quantitative viral load assays, and follow with prophylaxis with 3 months of oral ganciclovir or valganciclovir prophylaxis (based on creatinine clearance). This approach has resulted in rare symptomatic relapses and generally prevents emergence of antiviral resistance.

Numerous issues remain. As noted, the role of oral valganciclovir in treatment remains under investigation. This agent provides good bioavailability but is not approved for this indication. Some relapses occur in gastrointestinal disease because the assays used to follow disease are unreliable in this setting. Repeat endoscopy should be considered to ensure the clearance of infection. The optimal dosing of valganciclovir for *prophylaxis* in renal transplant recipients is also unclear. It is often worth measuring a formal creatinine clearance to ensure adequate dosing.

Alternative therapies are available in intravenous form only, including foscarnet and cidofovir. Foscarnet has been used extensively for therapy of CMV in AIDS patients. Although it is active against most ganciclovir-resistant strains of CMV, we prefer combination therapy (ganciclovir and foscarnet) for organ transplant recipients given the toxicities of high-dose, single-agent therapy, and given the antiviral synergy that has been reported.[45] Cidofovir has been used in renal transplant recipients, often with nephrotoxicity. Foscarnet and cidofovir may exhibit synergistic nephrotoxicity with calcineurin inhibitors. A newer class of agents (dihydroorotate dehydrogenase inhibitors [leflunamide]) that has been approved for immunosuppression and treatment of rheumatological diseases also seems to have useful activity against CMV (and possibly BK polyomavirus). Mirabavir is in clinical trials for CMV prophylaxis and therapy.

Epstein-Barr Virus

EBV is a ubiquitous herpesvirus that infects B lymphocytes. In immunosuppressed transplant recipients, primary EBV infection (and relapses in the absence of antiviral immunity) causes a mononucleosis-type syndrome, generally manifesting as a lymphocytosis (B cell) with or without lymphadenopathy or pharyngitis. 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.[46,49,51,53] The most clearly defined risk factor for PTLD is primary EBV infection, which increases the risk for PTLD by 10-fold to 76-fold. PTLD may occur, however, in the absence of EBV infection or in seropositive patients. 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% to 60%. Many deaths are associated with allograft failure after withdrawal of immunosuppression during treatment of malignancy. Compared with the general population, PTLD has increased extranodal involvement, poor response to conventional therapies, and poor outcomes. The spectrum of disease is broad and ranges from benign polyclonal, B cell, infectious mononucleosis–like disease to malignant, monoclonal lymphoma.[30] Most disease is of B cell origin although T cell, natural killer cell, and null cell tumors are described. EBV-negative PTLD has been described, and T cell PTLD has been shown in allografts thought to have rejection or other viral infection. PTLD late (>1 to 2 years) after transplantation is more often EBV-negative in adults. (See Chapter 33.)

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

- Unexplained fever (fever of unknown origin)
- 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 disease

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.[24,25,43,62] 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.

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 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 renal 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 [Oncovin], prednisone), or adoptive immunotherapy with stimulated T cells have been used.[11,17,28,67]

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 that in AIDS. Polyomaviruses are small nonenveloped viruses with covalently closed, circular double-stranded DNA genomes. Adult levels of seroprevalence are 65% to 90%. There seems to be a decrement of antibody positivity in adulthood. BK virus seems to achieve 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.[19,31,32,44,47,48,58,59] Active infection of renal allografts has been associated with progressive loss of graft function ("BK nephropathy") in approximately 4% of renal transplant recipients; this is referred to as polyomavirus-associated nephropathy (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. Polyoma-associated nephropathy manifested by characteristic histological features and renal dysfunction is found in about 1% to 8% of renal transplant patients.

Risk factors for nephropathy are poorly defined. Several risk factors have been implicated, although there is no consensus. Nickeleit and colleagues[48] found cellular rejection occurred more commonly in patients with BK nephropathy than controls. Other studies have implicated high-dose immunosuppression (particularly tacrolimus and mycophenolate mofetil), pulse-dose steroids, severe ischemia-reperfusion injury, exposure to antilymphocyte therapy, increased number of HLA mismatches between donor and recipient, deceased donor renal transplants, and presence and degree 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.

Diagnosis. 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.[19,32] It is a useful screening tool but cannot establish a firm diagnosis. The use of molecular techniques to screen blood or urine also has been advocated but is more useful in the management of established cases (viral clearance with therapy) than in specific diagnosis.[12,23,29,54,56,57] Hirsch and colleagues[32] showed that patients with BK nephropathy have a plasma viral load statistically significantly higher (>7700 BK virus copies per mL of plasma [P <.001; 50% positive predictive value, 100% negative predictive value]) than patients without such disease.

Given the presence of viremia in renal allograft recipients, it is crucial to reduce immunosuppression whenever possible. The possible coexistence of rejection and BK infection makes renal biopsy essential, however, for the management of such patients. Renal biopsy specimens initially show cytopathic changes in renal epithelial cells with the gradual evolution of cellular infiltration consistent with the diagnosis of interstitial nephritis. Fibrosis is often prominent occasionally with calcification. Immunostaining for cross-reacting SV40 virus shows patchy staining of viral particles within tubular cells.

Treatment. There is no accepted treatment for polyomavirus-associated nephropathy other than a reduction in the intensity of immunosuppression. It is possible to monitor the response to such maneuvers using urine cytology (decoy cells) and viral load measures in blood or urine or both. It is unclear whether reduction of calcineurin inhibitors or antimetabolites should be considered first. Given the toxicity of calcineurin inhibitors for tubular cells, and the role of injury in the activation of BK virus and the need for anti–BK T cell activity, we have generally reduced these agents first. Other centers have selected reduction of the antimetabolite first. Regardless of the approach, renal function, drug levels, and viral loads must be monitored carefully.

Some centers advocate the use of cidofovir for BK nephropathy in low doses (0.25 to 1 mg/kg every 2 weeks).[3,8,10,72] Significant renal toxicity may be observed with this agent, and may add little to reduction in immunosuppression alone. Retransplantation has been achieved in such patients with failed allografts—possibly reflecting immunity developing subsequent to discontinuation of immunosuppression.[52]

JC VIRUS

Infection of the central nervous system by JC polyomavirus has been observed uncommonly in renal allograft recipients as progressive multifocal leukoencephalopathy. This infection generally manifests with focal neurologic deficits or seizures and may progress to death after extensive demyelination. Progressive multifocal leukoencephalopathy may be confused with calcineurin neurotoxicity; both may respond to a reduction in drug levels. These are believed to be distinct entities, but further studies are under way.

Fungal Infections

In addition to the endemic mycoses, transplant recipients are at risk for opportunistic infection 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. 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 renal transplant recipients is candiduria, even if the patient is asymptomatic. Particularly 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 risk of visceral invasion of greater than 50% 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. Two species, *Aspergillus fumigatus* and *Aspergillus flavum*, account for most of these infections, although amphotericin-resistant isolates (*Aspergillus terreus*) occasionally are recognized. 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, central nervous system 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 débridement is usually essential for successful clearance of such invasive infections.

Cryptococcus neoformans *and Central Nervous System Infections*

Central nervous system infection in the transplant recipient may result from a broad spectrum of organisms. Infections are often metastatic to the central nervous system from the bloodstream 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 *S. 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 bloodstream (*Histoplasma* and *Pseudallescheria/Scedosporium, Fusarium*). Parasites include *T. gondii* and *Strongyloides*.

Given the spectrum of etiologies, precise diagnosis is essential. A reasonable empirical regimen would treat pneumococcus (ceftriaxone and vancomycin), *Listeria* (ampicillin), *Cryptococcus* (fluconazole or amphotericin), and herpes simplex virus (acyclovir) while awaiting data (lumbar puncture, blood cultures, and radiographic studies). Noninfectious etiologies, including calcineurin inhibitor toxicity, lymphoma, and metastatic cancer, should be included in the differential diagnosis. Molecular assays (HSV) and biopsy (for noninfectious etiologies) may be needed for diagnosis.

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.

DIAGNOSIS AND TREATMENT

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 and cryptococcal antigen studies. Initial treatment is probably best with liposomal amphotericin and flucytosine (after obtaining serum levels) followed by high-dose fluconazole until the cryptococcal antigen is cleared from blood and cerebrospinal fluid. Scarring and hydrocephalus may be observed.

Pneumocystis *and Fever with Pneumonitis*

The spectrum of potential pathogens of the lungs in the transplant recipient is too broad for this discussion. Some general concepts are worth mentioning, however. As for all infections in transplantation, invasive diagnostic techniques are often necessary in these hosts. 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*.[20,21]

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*.[37,38] CT of the chest is useful when the chest radiograph is negative or when the radiographic findings are subtle or nonspecific. 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.

The risk of infection with *Pneumocystis* is greatest in the first 6 months after transplantation and during periods of increased immunosuppression.[18,20,21] 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 *P. carinii (jiroveci)* 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 (jiroveci)* 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.[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. Chest CT scans are more sensitive to the diffuse interstitial and nodular pattern than routine radiographs. The clinical and radiological manifestations of *P. carinii (jiroveci)* 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 renal transplant patients tolerate full-dose trimethoprim/sulfamethoxazole for prolonged periods. This reflects the elevation of creatinine owing to 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. 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, Isospora belli, Cyclospora cayetanensis, Nocardia asteroides*, and common urinary, respiratory, and gastrointestinal bacterial pathogens. Alternative agents lack this spectrum of activity.

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