Infection in Renal Transplant Recipients

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Summary: Renal transplant recipients are susceptible to infection by a wide array of pathogens. Impaired inflammatory responses due to immunosuppressive therapies suppress clinical and radiologic findings engendered by microbial invasion. As a result, patients are often minimally symptomatic and evaluation and diagnosis are delayed. Specific microbiologic diagnosis is essential both for the optimization of antimicrobial therapy and to avoid unnecessary drug toxicities. Differential diagnosis is guided by knowledge of organisms commonly involved in infection in immunocompromised hosts and understanding of the limitations of prophylactic strategies. The risk of infection in the organ transplant recipient is determined by the interaction between the individual's epidemiologic exposures and net state of immunosuppression. Epidemiology includes environmental exposures in the community and hospital, organisms derived from donor tissues and latent infections activated in the host during immune suppression. The net state of immune suppression is determined by the interaction of all factors contributing to infectious risk. Routine antimicrobial prophylaxis is aimed at common infections and unique risk factors in individual patient groups. This includes trimethoprim-sulfamethoxazole (for Pneumocystis, Toxoplasma, most Nocardia and Listeria, common urinary pathogens), perioperative (eg, anti-fungal prophylaxis for pancreas transplants), or antiviral (for herpesviruses in high risk recipients).
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Transplant recipients are susceptible to a broad range of infectious pathogens. Patients often will have nonspecific symptoms, making distinction of infection from noninfectious processes (eg, graft rejection, drug toxicity) difficult. Successful management of infections in the transplant recipient is dependent on an understanding of the graft recipient's immune deficits and the nature and intensity of infectious exposures.[1] Management often is hampered by the toxicity of both antimicrobial and immunosuppressive regimens and by poor tolerance of invasive diagnostic procedures. However, an early and aggressive diagnostic approach is justified by the high morbidity and mortality of infection in this population.

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THE RISK OF INFECTION AFTER TRANSPLANTATION

The risk of infection in the renal transplant recipient is determined by the interaction of 2 factors: (1) the epidemiologic exposures of the patient including the timing, intensity, and virulence of the organisms to which the individual is exposed (Table 1); and (2) the patient's net state of immunosuppression, a measure of all host factors potentially contributing to the risk for infection (Table 2).

Consideration of these factors for each patient allows the development of a differential diagnosis for infectious syndromes for transplant recipients and also can be used to direct preventative strategies (prophylaxis, vaccination) that are appropriate to each individual's degree of risk for specific infections.

Epidemiologic Exposures

Exposures of importance can be divided into 4 overlapping categories: donor- or recipient-

Table 1. Significant Epidemiologic Exposures Relevant to Transplantation

Donor-derived
Viral
Herpes group (CMV, EBV, HHV-6, −7, −8, HSV)
Hepatitis viruses (notably B and C)
Retroviruses (HIV, human T-cell leukemia virus [HTLV]−1 and -2)
Lymphocytic choriomeningitis virus (LCMV)
Rabies
Bacteria
Gram-positive and gram-negative bacteria (*Staphylococcus* spp, *Pseudomonas* spp, Enterobacteriaeciae)
Mycobacteria (tuberculosis and nontuberculous)
Nocardia asteroides
Fungi
Candida spp (often azole-resistant)
Aspergillus spp
Endemic fungi (*C neoformans*)
Geographic fungi (*H capsulatum*, *C immitis*, *B dermatiditis*)
Parasites
Toxoplasma gondii
Trypanosoma cruzi
Nosocomial exposures
Methicillin-resistant *S aureus* (MRSA)
Vancomycin-resistant enterococci (VRE, also linezolid-, daptomycin-, and quinupristin/dalfopristin-resistant)
Aspergillus spp
Candida non-albicans strains
Community exposures
Food and water-borne (*L monocytogenes*, *Salmonella* spp, *Cryptosporidium* spp, hepatitis A, *Campylobacter* spp)
Respiratory viruses (RSV, influenza, parainfluenza, adenovirus, metapneumovirus)
Common viruses, often with exposure to children (coxsackievirus, parvovirus, polyomavirus, papillomavirus)
Atypical respiratory pathogens (*Legionella* spp, *Mycoplasma* spp, *Chlamydia*)
Geographic fungi and *Cryptococcus*, *P jiroveci*
Parasites (often distant)
Strongyloides stercoralis
Lesihmania spp
Toxoplasma gondii
Trypanosoma cruzi
Naeglaeria fowleri

derived infections, and community- or nosocomially derived exposures.

Donor-Derived Infections

Infections derived from donor tissues are recognized as increasingly important factors in transplantation, largely as the result of improved diagnostic testing.[2] The most common and well known are latent viral infections (eg, cytomegalovirus [CMV], or Epstein Barr virus [EBV]), which may activate in the transplant recipient. The greatest risk of these infections is to seronegative (immunologically naive) recipients who receive infected grafts from seropositive donors (carrying latent viral infection). Other donor-derived infections result from active, but unrecognized, infections in the donor at the time of procurement. This group includes individuals who are bacteremic or fungemic at the time of donation. These infections (staphylococci, *Streptococcus pneumoniae*, *Candida* species, *Salmonella*, *Escherichia coli*) may infect devitalized tissues or anastomotic sites (vascular, urinary), producing abscesses or mycotic aneurysms. Other latent in-

Table 2. 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 immune deficiency
Hypogammaglobulinemia (eg, from proteinuria)
Complement deficiencies
Autoimmune diseases (eg, systemic lupus erythematosus)
Other disease states: HIV, lymphoma/leukemia
Metabolic conditions: uremia, malnutrition, diabetes, cirrhosis
Immunomodulatory viral infection (CMV, HBV, HCV, and RSV)

Table 3. The Pretransplant Evaluation

Laboratory Test	All Patients	Patients With Exposure to Endemic Area	Quantitative Viral Studies Available (PCR)
Serologies			
CMV	√		√
HSV	√		√
VZV	√		
EBV	√		√
HIV	√		√
HBV: hepatitis B virus surface antigen (HBsAg)	√		√
antibody to hepatitis B virus surface antigen (anti-HBs)	√		
HCV	√		√
Treponema pallidum	√		
T gondii	√		
S stercoralis		√	
Leishmania spp		√	
T cruzi		√	Blood smear
H capsulatum		√	
C neoformans		√	Cryptococcal antigen
C immitis		√	
Other studies			
Urinalysis and culture	√		
Skin test: Mantoux skin test (PPD)	√		
Chest radiograph (routine)	√		
Stool examination for ova and parasites (*Strongyloides*)		√	
Urine ova and parasites ± cystoscopy		√ (for kidneys)	Schistosomiasis endemic areas

fections, such as tuberculosis, may activate many years after the initial exposure.

Donor screening for transplantation is limited by the available technology (approved for use in donor screening) and by the time available within which organs from deceased donors must be used. At present, the routine evaluation of donors generally relies on antibody detection (serologic) tests and microbiologic cultures to detect common infections (Table 3).[3-9] As a result, some active infections remain undetected because seroconversion may not occur during acute infection. Thus, some organs inevitably will be implanted that carry unidentified pathogens. This risk is shown by recent clusters of donor-derived *Trypanosoma cruzi* (Chagas' disease), rabies virus, West Nile virus, and lymphocytic choriomeningitis virus infections in organ transplant recipients.[10]

Given the risk of transmission of infection from the organ donor to the recipient, certain infections should be considered relative contraindications to organ donation (Table 4). Because renal transplantation generally is an elective surgery, it is reasonable to avoid donation from individuals with unexplained fever, rash, or infectious syndromes, particularly those affecting the central nervous system.

Recipient-Derived Exposures

Infections in this category reflect colonization or latent infections that reactivate in the setting of immune suppression.[11,12] A careful history of travel and exposures guides preventative ap-

Table 4. Common Infectious Exclusion Criteria for Organ Donors

CNS Infection
Undiagnosed infection of central nervous system (encephalitis, meningitis)
Herpes simplex 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 (serologic or molecular)
HSV (with active viremia), acute EBV (mononucleosis)
Serologic or molecular evidence of HTLV-I/II
Active hepatitis A or hepatitis B
Parasitic infections: *T cruzi*, *Leishmania donovani*, *S stercoralis*, *T gondii*
Infections difficult to treat while on immunosuppression
Active tuberculosis
SARS
Untreated pneumonia
Untreated bacterial or fungal sepsis (eg, candidemia)
Untreated syphilis
Multisystem organ failure caused by overwhelming sepsis, gangrenous bowel

NOTE. The use of these exclusion criteria must be considered in the context of the individual donor/recipient.

proaches and empiric therapies. Notable among these infections are mycobacterial infections (including tuberculosis), strongyloidiasis, viral infections (herpes simplex and varicella zoster virus [VZV] or shingles), histoplasmosis, coccidioidiomycosis, hepatitis B virus (HBV) or hepatitis C virus (HCV), and human immunodeficiency virus (HIV).[13,14] Vaccination status should be evaluated (tetanus, hepatitis B, childhood vaccines, influenza, pneumococcus) and include special risks (eg, hepatitis A or yellow fever vaccines in advance of transplantation for travelers). Dietary habits should be considered such as the use of well water (*Cryptosporidium*), uncooked meats (*Salmonella*, *Listeria*), and unpasteurized dairy products (*Listeria*).

Community Exposures

Common exposures in the community may be caused by contaminated food or water, infected family or coworkers, or exposure as a result of travel or work. Infection caused by common respiratory viruses (influenza, respiratory syncytial virus [RSV], and adenovirus) and with atypical pathogens in adults (eg, VZV from children) carries the risk of viral pneumonia and secondary bacterial or fungal superinfections. Community (contact- or transfusion-associated) exposure to CMV and EBV may produce severe primary infection in the nonimmune host. Recent or 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 with immunosuppressive therapy. *Strongyloides* reactivation may cause diarrheal illness, progressing to hyperinfestation syndrome (parasite migration with hemorrhagic enterocolitis or hemorrhagic pneumonia) or disseminated infection with accompanying gram-negative or

Table 5. Immune Suppression 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, PCP, HBV, HCV
Azathioprine: neutropenia, papillomavirus?
Mycophenylate 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

polymicrobial bacteremia or meningitis. Gastroenteritis caused by *Salmonella* species in the transplant recipient may be associated with bloodstream invasion and metastatic infection.

Nosocomial Exposures

Nosocomial infections may manifest in the early postsurgical period or later, in colonized patients during periods of intensified immune suppression. Antimicrobial-resistant strains include vancomycin-, linezolid-, and quinupristin/dalfopristin-resistant enterococci, methicillin-resistant Staphylococci, and fluconazole-resistant *Candida* species. *Aspergillus* infection in a compromised host should provoke examination of infection control practices. Antimicrobial abuse in critically ill patients is reflected in high rates of *C difficile* colitis. Respiratory viral infections may be acquired from medical staff and should be considered among the causes of fever and respiratory decompensation among hospitalized or institutionalized immunocompromised individuals. Each nosocomial 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 both immunosuppressive medications and iatrogenic conditions (Table 2). Among the most important are the following: (1) specific immunosuppressive therapies, including the dose, duration, and sequence of agents; (2) technical difficulties during transplant surgery, with resulting fluid collections (blood, lymph, urine), devitalized tissue, and wound infections; (3) prolonged instrumentation including airway intubation and the use of vascular access devices; (4) broad-spectrum antimicrobial agents; (5) renal and/or hepatic dysfunction (in addition to graft dysfunction); and (6) presence of infection with one of the immunomodulating viruses, including CMV, EBV, HBV or HCV, or HIV.

Specific immunosuppressive agents are associated with increased risk for certain infections (Table 5).

TIMETABLE OF INFECTION

With standardized immunosuppressive regimens, specific infections vary in a predictable pattern depending on the time elapsed since transplantation (Fig. 1). This is primarily a reflection of the changing risk factors over time including surgery/hospitalization, immune suppression, acute and chronic rejection, emergence of latent infections, and exposures to novel community infections. The pattern of infection changes with the immunosuppressive regimen (eg, pulse dose steroids or intensification for graft rejection), intercurrent viral infections, neutropenia, or significant epidemiologic exposures (travel or food). The timeline remains a useful starting point, although it has been altered by the introduction of newer immunosuppressive agents and patterns of use, 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- and HCV-infected individuals, and broader epidemiologic exposures (eg, travel).

Fig. 1 shows 3 overlapping periods of risk for infection after transplantation, each most often associated with unique groups of pathogens. The perioperative period to approximately 4 weeks after transplantation reflects surgical and technical complications. The period 1 to 6 months after transplantation (depending on the rapidity of taper of immune suppression and the use of antilymphocyte induction therapy) reflects intensive immune suppression with viral activation and opportunistic infections. The period beyond 6 to 12 months after transplantation reflects community-acquired exposures and some unusual pathogens based on the level of maintenance immune suppression.

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

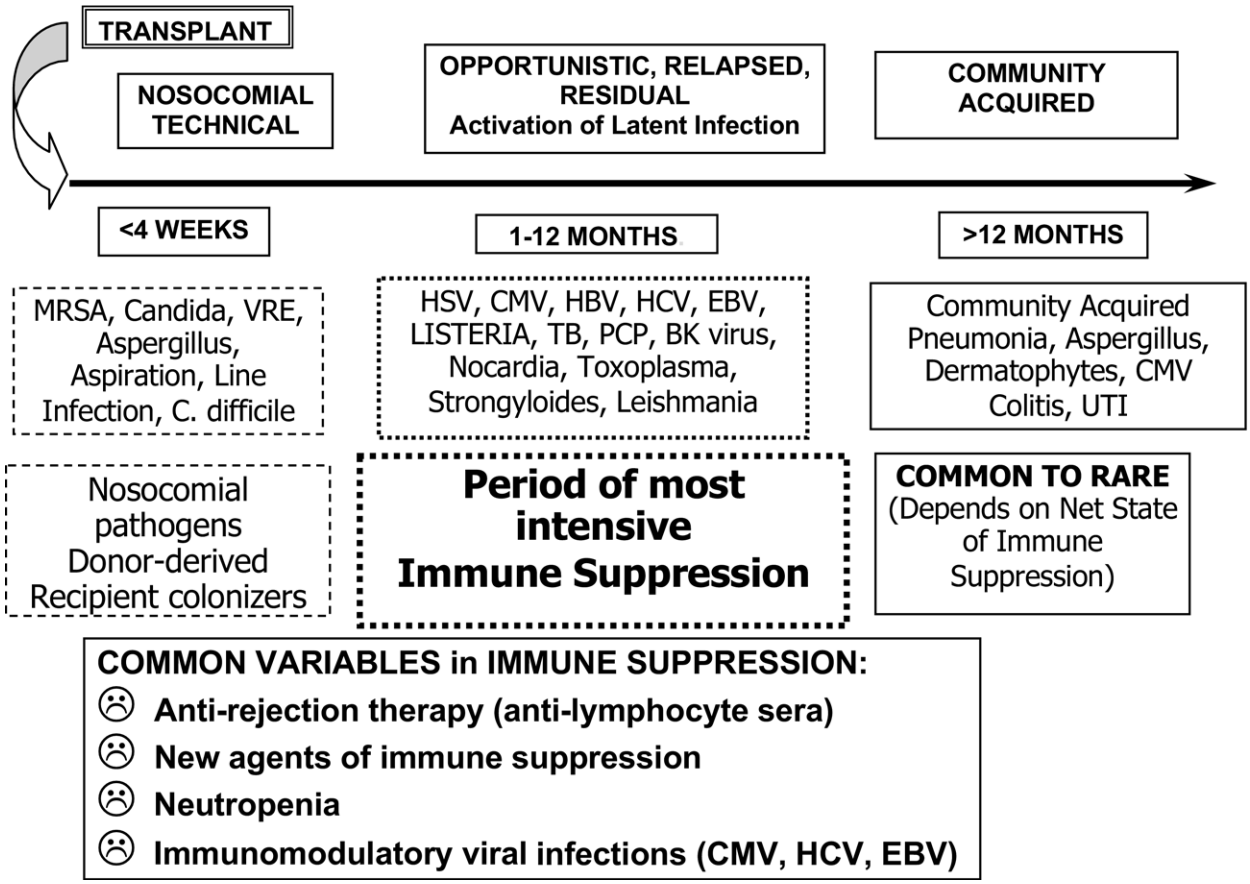

Figure 1. The timeline of infection after transplantation.

The prevention of infection must be linked to the risk for infection at various times after transplantation. One approach (used at the Massachusetts General Hospital) is outlined in Table 6, but should be adapted to the specific needs of institutions based on local experience. It should be noted that such strategies serve only to delay the onset of infection in the face of epidemiologic pressure. The use of antibiotic prophylaxis, vaccines, and behavioral modifications (eg, routine hand washing or advice against digging in gardens without masks) may result in only a shift to the right of the infection timeline unless the intensity of immune suppression is reduced or immunity develops.

The First Phase: First Month After Transplantation

During the first month after transplantation, 3 types of infections occur. The first is infection present in the recipient before transplantation that emerges in the setting of surgery, anesthesia, 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 (eg, methicillin-resistant *Staphylococcus aureus*). All infections should be controlled or eradicated before transplantation.

The second type of early infection is donor-derived (described previously). Donor-derived infections emerge earlier than would be anticipated for the same pathogens in normal hosts. Thus, atypical syndromes (encephalitis, hepatitis, and pneumonia) may be a clue to the presence of donor-derived infection if there is no epidemiologic hazard and/or no (common) pathogen identified to account for the process. Such infections may require epidemiologic in-

Table 6. Routine Antimicrobial Protocols for Renal Transplantation at Massachusetts General Hospital, Boston, MA

Pretransplant

Routine vaccinations to be brought up to date including: Measles/mumps/rubella, Diphtheria/tetanus/pertussis, Poliovirus, *Haemophilus influenzae* b, hepatitis B, *Pneumococcus*, influenza, varicella

***Pneumocystis carinii* (*jirovecii*) pneumonia (PCP) and general antibacterial prophylaxis**

Regimen: one single strength trimethoprim-sulfamethoxazole tablet (containing 80 mg trimethoprim, 400 mg sulfamethoxazole) orally every day for a minimum of 4 to 6 months posttransplant. Patients infected with CMV, with chronic rejection, or recurrent infections are maintained on lifelong prophylaxis. A 3 times/wk regimen of trimethoprim-sulfamethoxazole will prevent PCP, but will not prevent other infections (eg, urinary tract infections, *Nocardia*, *Listeria*, *Toxoplasma*, and other gastrointestinal/pulmonary infections).

Alternative regimen: for those patients proven not to tolerate trimethoprim-sulfamethoxazole, alternative regimens include: (1) a combination of atovaquone 1,500 mg orally 4 times a day with meals plus levofloxacin 250 mg orally every day (or equivalent fluoroquinolone without antianaerobic activity); (2) pentamidine (300 mg intravenously or inhaled every 3-4 weeks); (3) Dapsone (100 mg orally every day or twice weekly) ± pyrimethamine. Each of these agents has toxicities that must be considered (eg, hemolysis in G6PD-deficient hosts with dapsone). None of these alternative programs offers the same broad protection of trimethoprim-sulfamethoxazole.

CMV Prophylaxis

CMV serostatus ± ALT	Therapy*	Screening (antigenemia)
D+/R−	Ganciclovir 5 mg/kg intravenously for loading dose then per renal function to discharge; then valganciclovir (900 mg orally every day corrected for renal function --> generally 450 mg/d for renal transplants) × 3 mo	Monthly for 6 months after D/C of therapy†
D+ or R+ with ALG	Ganciclovir 5 mg/kg intravenously for first dose then per renal function to discharge; valganciclovir daily × 6 mo	Monthly for 6 months after D/C of therapy†
D−/R+ (no ALG)	Valganciclovir (dosed as above) × 3 mo	Symptoms only
D−/R−	Famciclovir 500 mg orally every day × 3-4 months (or valacyclovir 500 twice a day or acyclovir 400 3 times/day) Use of CMV-negative or leukocyte-reduced blood	Symptoms, fever/neutropenia
Status unknown with ALG	Ganciclovir 5 mg/kg intravenously for first dose and every day (corrected for renal function) until serostatus determined	

Neutropenia: The dose of antiviral and antibacterial therapies are not, in general, reduced for neutropenia. Consider other options first.

*NOTE. Not approved by the Food and Drug Administration at these doses.

†ALG: Antilymphocyte globulin therapy: includes any of the lytic, lymphocyte-depleting antisera.

Fungal Prophylaxis

Prevention of mucocutaneous Candidiasis can be accomplished with oral clotrimazole or nystatin 2 to 3 times per day at times of steroid therapy or in the face of broad-spectrum antibacterial therapy and in diabetic transplant patients. 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.

vestigation with public health authorities and organ-procurement organizations.

The third and most common source of infections in the early period is that related to the complex surgical procedure of transplantation. These include surgical wound infections, pneumonia (aspiration), bacteremia caused by vascular access or surgical drainage catheters, urinary tract infections, or infections of fluid collections—leaks of vascular or urinary anastomoses or of lymphoceles. These are nosocomial infections and, as such, are caused by the same antimicrobial-resistant bacteria and *Candida* infections observed in nonimmunosuppressed patients undergoing comparable surgery. However, given immune suppression, signs of infection may be subtle and the severity greater. The technical skill of the surgeons and meticulous postoperative care (ie, wound care and proper maintenance including timely removal of endotracheal tubes, vascular access devices, and drainage catheters) are the main determinants of risk for these infections. Also among the common infections is *C difficile* colitis.

Limited perioperative antibiotic prophylaxis usually is adequate, with additional coverage only for known risk factors (eg, prior colonization with methicillin-resistant *S aureus*). For pancreas transplantation, perioperative prophylaxis against yeasts is provided using fluconazole, mindful of potential increases in sirolimus/calcineurin inhibitor levels with azole antifungal agents.

Notably absent in the first month after transplantation are opportunistic infections, even though the intensity of immunosuppressive therapy is greatest. This observation illustrates the role of the cumulative effect of these drugs—the area under the curve—in determining the true state of immunosuppression. Thus, opportunistic infection in this period should trigger an epidemiologic investigation for an environmental hazard.

The Second Phase: 1 to 6 Months After Transplantation

Infection in the transplant recipient 1 to 6 months after transplantation has 1 of 3 causes.

The first group includes residual infection from the perisurgical period including *C difficile* colitis or pneumonia or technical problems (eg, urinoma, lymphocele, hematoma). Fluid collections in this setting generally require drainage.

The second group includes viral infections including CMV, herpes simplex virus (HSV), shingles (VZV), human herpesvirus 6 or 7, EBV, or hepatitis (HBV, HCV). This group of viruses is unique. These infections are lifelong and tissue-associated (often transmitted with the allograft from seropositive donors). More importantly, these viruses are systemically immune suppressive and predispose to graft rejection. Other viral pathogens of this period include BK polyomavirus (in association with allograft dysfunction) and community-acquired respiratory viruses (adenovirus, influenza, parainfluenza, RSV, and metapneumovirus).

The third group includes opportunistic infection caused by *Pneumocystis carinii* (*jiroveci*), *Listeria monocytogenes*, *Toxoplasma gondii*, *Nocardia* species, *Aspergillus* species, and other agents.

Viral pathogens (and rejection) are responsible for the majority of 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 (discussed later) (Table 6). Trimethoprim-sulfamethoxazole prophylaxis effectively prevents *P jiroveci* pneumonia (PCP) and reduces the incidence of urinary tract infections and urosepsis, *L monocytogenes* meningitis, *Nocardia* species infection, and *T gondii*.

The Third Phase: More Than 6 to 12 Months After Transplantation

Transplant recipients who are more than 6 months posttransplant can be categorized into 3 groups in terms of infectious risk. The majority of transplant recipients (70%-80%) have a technically good procedure with satisfactory allograft function and reduced immunosuppression. These patients resemble the general community in terms of infectious risk, with community-acquired respiratory viruses constituting a major risk.

A second group of patients suffers chronic viral infection, which in the absence of effective antiviral therapy (often reduction in immune sup-

pression) produces end organ damage (eg, BK polyomavirus leading to nephropathy, HCV leading to cryoglobulinemia or cirrhosis, and CMV with chronic graft rejection) and malignancy (posttransplantation lymphoproliferative disease [PTLD] caused by to EBV, and skin or anogenital cancer caused by papillomaviruses).

A third group of patients has less than satisfactory allograft function and receives more intensive immunosuppressive therapy to preserve graft function. Even minimal signs or symptoms merit careful evaluation in this group of high-risk individuals.

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 (computerized tomography [CT] or magnetic resonance imaging scanning and molecular microbiologic techniques) may greatly assist in this process. However, the need for invasive diagnostic tools cannot be overemphasized. 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 will be broad by necessity, with a rapid narrowing of the antimicrobial spectrum as data become available.

With acute infection in patients not yet at minimal levels of immunosuppression, it may be reasonable to reduce the intensity of immune suppression with the understanding that such an approach carries the risk of graft rejection. This may be most useful for patients with activation of latent viral infections (CMV, EBV, or BK), histoplasmosis, or tuberculosis, in whom infection should be seen as evidence of excessive immune suppression. Immune suppression may be re-instituted once microbiologic evidence of control of infection (eg, viral load, antigen assays) is shown. In contrast, for intercurrent bacterial or fungal infections, reductions in immune suppression can be considered in individuals who are unresponsive to initial therapy or in those receiving higher than maintenance levels of corticosteroids. Co-infection with virus (CMV) is common and merits additional therapy.

Viral Pathogens

CMV

CMV is the single most important pathogen in transplant recipients, having a variety of direct and indirect effects.[15-19] The direct effects include the following: (1) fever and neutropenia syndrome with features of infectious mononucleosis, including hepatitis, nephritis, leukopenia, and/or thrombocytopenia; (2) pneumonia; (3) gastrointestinal invasion with colitis, gastritis, ulcers, bleeding, or perforation; (4) hepatitis, pancreatitis; and (5) 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 begin until later in the transplant course.

The indirect effects of viral infection also are important. CMV infection produces a profound suppression of a variety of host defenses, predisposing to secondary invasion by such pathogens as *Pneumocystis*, *Candida*, and *Aspergillus* species, and some bacteria. CMV also contributes to the risk for graft rejection, PTLD, human herpesvirus (HHV)6 and HHV7 infections, and acceleration of HCV infection. The mechanisms for these effects are complex, including alteration of T-cell numbers and functions 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 1 of 3 patterns: primary infection, reactivation, and superinfection.

Primary CMV Infection. Primary infection occurs most often when seronegative individuals receive grafts from latently infected, seropositive donors (donor seropositive, recipient seronegative [D+R−]), with subsequent reactivation of the virus and systemic dissemination after transplantation. Between 40% and 50%

of these patients experience direct infectious disease manifestations of CMV although the majority 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 CMV Infection. In reactivation infection, seropositive individuals reactivate endogenous virus after transplantation (donor seropositive or seronegative, recipient seropositive (R+). When conventional immunosuppressive therapy is used (eg, no antilymphocyte antibody treatment), approximately 10% to 15% experience direct infectious disease syndromes, with a higher rate with the use of induction antilymphocyte therapy. Up to 50% of these individuals are viremic, often without symptoms.

CMV 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.[20,21] 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 antibodies, both polyclonal and monoclonal, 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, and cyclophosphamide are moderately potent in terms of promoting viral reactivation. These agents also perpetuate infection once it is established.

Allograft rejection is a major stimulus for CMV activation and vice versa. Thus, CMV infection has been linked to a diminished outcome of renal and other allografts. Reinke et al[19] showed that 17 of 21 patients for whom a biopsy examination 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.[22,23]

Diagnosis

Clinical management of CMV, both prevention and treatment, is important for the transplant recipient. It is based on understanding the causes of CMV activation and the available diagnostic techniques. CMV cultures are generally too slow and insensitive for clinical use. Further, 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. Serologic 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 immunoglobulin M 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. However, seroconversion in transplantation generally is delayed and thus is not useful for clinical diagnosis.[24] 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.[25,26] 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 [PCR], hybrid capture, and amplification assays) are highly specific and sensitive for the detection of viremia. Most commonly used assays include plasma-based PCR testing and the whole-blood hybrid capture assay. Note that whole-blood and plasma-based assays cannot be compared directly. The highest viral loads often are associated with tissue-invasive disease, with the lowest in asymptomatic CMV infection. Viral loads in the CMV syndrome are variable. Either assay

can be used in management. The central role of assays is illustrated by the approach to management of CMV prevention (Table 6). The schedule for screening is linked to the risk for infection. Thus, 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.

The advent of quantitative assays for the diagnosis and management of CMV infection has allowed a noninvasive diagnosis in many patients with 2 important exceptions: neurologic disease, including chorioretinitis, and gastrointestinal disease, including invasive colitis and gastritis. In these syndromes, the CMV assays often are negative and invasive diagnosis (biopsy) may be needed.

CMV Prevention

Prevention of CMV infection must be individualized. Two strategies are used commonly for CMV prevention: universal prophylaxis and pre-emptive therapy. Universal prophylaxis involves giving antiviral therapy to all at-risk patients beginning at or immediately posttransplant for a defined time period. In pre-emptive therapy, quantitative assays are used to monitor patients at predefined intervals 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 preventing not only CMV infection during the period of greatest risk, but also diminishing infections caused by HHV6, HHV7, and EBV. Further, the indirect effects of CMV (ie, graft rejection and opportunistic infections) also may be reduced by routine prophylaxis.[22,23,27,28] In practice neither strategy is perfect. Infrequently, breakthrough disease and ganciclovir resistance have been observed with both approaches.[23]

Given the risk for invasive infection, patients at risk for primary infection (CMV D+/R−) generally are given prophylaxis for 3 to 6 months after transplantation. Other groups may be candidates for pre-emptive therapy if an appropriate monitoring system is in place and patient compliance is good. However, current data support the use of universal prophylaxis (not pre-emptive therapy) in the prevention of indirect effects of CMV infection including PTLD, opportunistic infections, allograft rejection, and mortality.

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 dose adjustments for renal dysfunction) until a quantitative assay for CMV is negative. It often is worth measuring a formal creatinine clearance to ensure adequate dosing. 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 3-4 wk) may be useful. Prophylaxis for 2 to 3 months may reduce the risk for relapse in high-risk individuals. Relapses occur, primarily in those not treated beyond the achievement of a negative quantitative assay. The use of completely oral regimens for treatment is under study. Some relapses occur in gastrointestinal disease because the assays used to follow up disease are not reliable in this setting. Thus, repeat endoscopy should be considered to ensure the clearance of infection.

Alternative therapies are available in intravenous form only: foscarnet and cidofovir. Foscarnet has been used extensively for therapy of CMV in acquired immune deficiency syndrome patients. Both foscarnet and cidofovir may show synergistic nephrotoxicity with calcineurin inhibitors. A newer class of agents (dihydroorotate dehydrogenase inhibitors, ie, leflunamide), may have some useful activity against CMV (and possibly BK polyomavirus). Mirabavir is in clinical trials for CMV prophylaxis and therapy.

EBV

Primary EBV infection (and relapses in the absence of immunity) causes a mononucleosis-type syndrome, generally presenting 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 immune suppression. Regardless of its mode of expression, this syndrome should suggest relative overimmune suppression.

EBV also plays a central role in the pathogenesis of posttransplant lymphoproliferative disorder or PTLD.[29-32] Posttransplant non-Hodgkin's lymphoma is a common complication of solid-organ transplantation. The spectrum of disease is broad and ranges from benign polyclonal B-cell infectious mononucleosis-like disease to malignant monoclonal lymphoma. The most clearly defined risk factor for PTLD is primary EBV infection. Compared with the general population, PTLD has increased extranodal involvement, poor response to conventional therapies, and poor outcomes. The majority is of B-cell origin, although T-cell, natural killer cell, and null cell tumors are described. It should be noted that EBV-negative PTLD has been described and that T-cell PTLD has been shown in allografts from patients thought to suffer from rejection or other viral infection. PTLD late (>1-2 y) after transplantation is more often EBV-negative in adults.

The clinical presentations of EBV-associated PTLD vary, including: (1) unexplained fever (fever of unknown origin); (2) a mononucleosis-type syndrome with fever, malaise, with or without pharyngitis or tonsillitis (often diagnosed incidentally in tonsillectomy specimens), often no lymphadenopathy is observed; (3) gastrointestinal bleeding, obstruction, perforation; (4) abdominal mass lesions; (5) infiltrative disease of the allograft; (6) hepatocellular or pancreatic dysfunction; and (7) central nervous system disease.

Diagnosis. Serologic testing is not useful for the diagnosis of acute EBV infection or PTLD in transplantation. Thus, quantitative EBV viral load testing is required for the diagnosis and management of PTLD.[33] Serial assays are more useful in an individual patient than specific viral load measurements. These assays are not standardized and cannot be compared directly between centers. There are some data to 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 the 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 use given the viremia and role of EBV as an immune suppressive agent. With the progression of disease to extranodal and monoclonal malignant forms, reduction in immune suppression may be useful, but other therapies including anti–B-cell therapy (anti-CD20 rituximab), chemotherapy (CHOP), and/or adoptive immunotherapy have been used. In renal transplantation, the failure to regress with significant reductions in immune suppression may suggest the need to sacrifice the allograft for patient survival.

Polyomaviruses

Polyomaviruses are small nonenveloped viruses with covalently closed, circular, double-stranded DNA genomes. Adult levels of seroprevalence are 65% to 90%. 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 polyoma virus) similar to that in acquired immune deficiency syndrome. BK virus achieves latency in renal tubular epithelial cells. JC polyoma virus also has been isolated from renal tissues but appears to have preferred tropism for neural tissues. Reactivation occurs with immune deficiency and suppression and tissue injury (eg, ischemia-reperfusion).

BK Polyomavirus Infection. BK virus is associated with a range of clinical syndromes in immunocompromised hosts: viruria and viremia, ureteral ulceration and stenosis, and hemorrhagic cystitis. Active infection of renal allografts has been associated with progressive loss of graft function (BK nephropathy) in approximately 4% of renal transplant recipients.[34-37] This is referred to as *polyomavirus-associated nephropathy*.[36,38,39] BK nephropathy rarely is 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. Most cases present with diminished renal allograft function or with ureteric stenosis and obstruction. In such patients, the causes of decreased renal function must be evaluated carefully (eg, mechanical obstruction, drug toxicity, pyelonephritis, rejection, thrombosis, recurrent disease) and choices must be made between increasing immune suppression to treat suspected graft rejection or reducing immune suppression to allow the immune system to control infection. Biopsy examinations are essential for initial diagnosis. The course of therapy may be followed by quantitative molecular viral assays.[40,41] Patients with BK nephropathy treated with increased immune suppression have a high incidence of graft loss. Reduced immune suppression may stabilize renal allograft function but risks graft rejection. Polyoma-associated nephropathy manifested by characteristic histologic features and renal dysfunction is found in about 1% to 8% of renal transplant patients. Several risk factors for nephropathy have been implicated, although there is no consensus. Nickeleit et al[42] 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 human leukocyte antigen mismatches between donor and recipient, cadaver renal transplants, and presence and degree of viremia in the pathogenesis of disease. The role of specific immunosuppressive agents has not been confirmed. Of note, the greatest incidence of BK nephropathy is at centers with the most intensive immune suppressive 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. Therefore, 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 is specific diagnosis.[40-43] Hirsch et al showed that patients with BK nephropathy have a plasma viral load statistically significantly higher (>7,700 BK virus copies/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 useful to reduce immune suppression whenever possible. However, such reductions may provoke graft rejection and some centers report possible co-existence of rejection with BK infection, making renal biopsy essential for management. 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 often is 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 immune suppression. It is possible to monitor the response to such maneuvers using urine cytology (decoy cells) and viral load measures in blood and/or urine. Thus, it is unclear whether reduction of calcineurin inhibitors or antimetabolites should be considered 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 (0.25-1 mg/kg every 2 weeks). Of note, significant renal toxicity may be observed with this agent, especially in combination with the calcineurin inhibitors. Retransplantation has been achieved in patients with failed allografts after a period of time free of immune suppression (~6 mo), possibly as a reflection of immunity developing subsequent to reduction in immune suppression.[44,45]

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 presents with focal neurologic deficits or seizures and may progress to death after extensive demyelination. Progres-

sive multifocal leukoencephalopathy (PML) may be confused with calcineurin neurotoxicity; both may respond to a reduction in drug levels. It is thought that these are distinct entities but further studies are underway.

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* species, *Aspergillus* species, *Pneumocystis* (*carinii*) *jirovecii*, and *C neoformans*. Only the latter 2 are considered here. As a general consideration, more than half of *Candida* blood isolates are now from non-*albicans* species—with a significant risk of resistance to fluconazole therapy. Routine susceptibility testing should be obtained for any important yeast infections.

Cryptococcus neoformans and Central Nervous System Infections

Central nervous system (CNS) infection in the transplant recipient may result from a broad spectrum of organisms. Infections often are metastatic to the CNS from the bloodstream and lungs. Viral causes include CMV (nodular angiitis), herpes simplex meningoencephalitis, JC virus (PML), 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* species. Brain abscess and epidural abscess have been observed and may be particularly problematic when caused by methicillin-resistant *Staphylococcus aureus*, penicillin-resistant *Pneumococcus*, and quinolone-resistant *Streptococci*. Fungi may be metastatic from lungs (*Aspergillus* and *Cryptococcus*), but may also spread from sinuses (*Mucoraceae*), skin (*Dematiaceae*), and the bloodstream (*Histoplasma* and *Pseudoallescheria/Scedosporium, Fusarium* species). Parasites include *T gondii* and *Strongyloides*. Given the spectrum of etiologies, precise diagnosis is essential. Noninfectious etiologies including calcineurin inhibitor toxicity, lymphoma, and metastatic cancer should be included in the differential. Molecular assays (HSV) and biopsy (for noninfectious causes) may be needed for diagnosis.

Cryptococcal infection is seen rarely 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. Skin involvement at sites of tissue injury (catheters) also has been reported. Pneumonia and meningitis are common in the more intensively suppressed host.

Diagnosis and Treatment. Cryptococcosis should be suspected in transplant recipients who present with unexplained headaches, a decreased state of consciousness, failure to thrive, or unexplained focal skin disease. Diagnosis often is achieved by serum cryptococcal antigen detection, but all such patients should have lumbar puncture for cerebrospinal fluid cell counts and cryptococcal antigen studies. Initial treatment is probably best with liposomal amphotericin and 5-flucytosine (following 5-FC serum levels), followed by high-dose fluconazole until the cryptococcal antigen is cleared from the 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. However, some general concepts are worth mentioning. As for all infections in transplantation, invasive diagnostic techniques often are 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. 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 for the definition of the extent of the disease process, the possibility of simultaneous processes (superinfection), and for the selection of the optimal invasive technique to achieve pathologic diagnosis.

The risk of infection with *Pneumocystis* is

greatest in the first 6 months after transplantation and during periods of increased immune suppression.[46-48] 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 posttransplant. The expected mortality caused by *Pneumocystis* pneumonia is increased in patients on cyclosporine when compared with other immunocompromised hosts.

The hallmark of infection caused by *P carinii* (*jiroveci*) is the presence of marked hypoxemia, dyspnea, and cough with a paucity of physical or radiologic findings. In the transplant recipient, *Pneumocystis* pneumonia generally is acute to subacute in development. Atypical *Pneumocystis* infection (radiographically or clinically) may be seen in patients who have co-existing pulmonary infections or who develop disease while receiving prophylaxis with second-choice agents (eg, pentamidine or atovaquone). Patients outside the usual period of greatest risk for PCP may present with indolent disease, which may be confused radiographically with heart failure. A number of patients have been identified with interstitial pneumonitis while receiving rapamycin.[49] This syndrome may occur in the presence or absence of concomitant infections (adenovirus, RSV, *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 lactic dehydrogenase is increased in most patients with *Pneumocystis* pneumonia (>300 international units/mL). However, many other diffuse pulmonary processes also increase serum lactic dehydrogenase levels. No diagnostic pattern exists for *Pneumocystis* pneumonia on routine chest radiograph. The chest radiograph may be entirely normal or develop 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 radiologic manifestations of PCP are virtually identical to those of CMV. Indeed, the clinical challenge is to determine whether both pathogens are present. Significant extrapulmonary disease is uncommon in the transplant recipient.

Early therapy, preferably with trimethoprim-sulfamethoxazole is preferred; few renal transplant patients will tolerate full-dose trimethoprim-sulfamethoxazole for prolonged periods of time. This reflects both the increase of creatinine caused 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. Alternate 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 immune suppression generally is considered a part of anti-infective therapy in transplantation, the use of short courses of adjunctive steroids with a gradual taper generally is 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 useful in the patient with significant allergy to sulfa drugs. Trimethoprim-sulfamethoxazole is the most effective agent for prevention of infection caused by *P jiroveci.* The advantages of trimethoprim-sulfamethoxazole include increased efficacy, lower cost, the 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. It should be noted that alternative agents lack this spectrum of activity.

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