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CHAPTER 101

Medical Management of the Kidney Transplant Recipient: Infections and Malignant Neoplasms

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Patient and graft survival rates in recipients of solid organ transplants have improved significantly because of refinement in surgical techniques and the advent of potent immunosuppressive agents. Nonetheless, malignant neoplasms and infectious complications continue to adversely affect post-transplantation morbidity and mortality. Although rare, donor-derived infections or malignant disease can arise by delayed donor seroconversion after a recent acute infection, unidentified pathogens in the organ donor, occult neoplastic disease at the time of organ procurement, or malignant transformation of donor cells. This chapter discusses infections and post-transplantation–related malignant neoplasms in recipients of renal transplants. Post-transplantation infectious and drug-related gastrointestinal complications are also discussed.

INFECTIOUS DISEASES

Despite prophylactic therapy against common bacterial, viral, and opportunistic pathogens in the perioperative and postoperative period, infections are the second most common cause of death after cardiovascular disease (CVD) in renal transplant recipients. According to the U.S. Renal Data System (USRDS), infections occurred at a rate of 45 per 100 patient-years during the first 3 years after transplantation.[1] The most common infections are bacterial, followed by viral and fungal. Parasitic infections are rare. Notably, cytomegalovirus (CMV) and herpes simplex virus (HSV) infection rates have decreased since the mid-1990s as a result of effective antiviral prophylaxis; hepatitis B virus (HBV) and hepatitis C virus (HCV) infection rates increased during the same period for unclear reasons.

Infectious Etiologies

Both the type and occurrence of infections in the immunocompromised transplant recipient follow a "timetable pattern" (Fig. 101.1).[2]

Infection with Transplantation

Although rare, both blood-borne and kidney infections have been transmitted during donation. These include viral infections (e.g., HCV, HBV, human immunodeficiency virus (HIV), CMV, and BK, among others), parasitic infections (malaria, *Babesia*), and bacterial infections (from undiagnosed bacteremia or renal infections).

Month 1 After Transplantation

Most infections in the first month are due to common bacteria and *Candida* acquired in the hospital setting. Except for HSV, other viral infections are uncommon during this period. Similar to those that follow any major surgical procedure, most bacterial infections during this period involve wounds, catheters, and drainage sites. Aspiration pneumonia and urinary tract infections (UTIs) are common. Infections specific to renal transplant recipients include perinephric fluid collections due to lymphoceles, wound hematomas, or urine leaks; indwelling urinary stents; and UTIs secondary to urinary tract abnormalities, such as ureteral stricture, vesicoureteral reflux, or neurogenic bladder. Most UTIs are caused by common gram-negative bacteria (*Escherichia coli*, Enterobacteriaceae, and *Pseudomonas)* and gram-positive bacteria (enterococcus). Preventive measures for UTIs include early urethral catheter removal and antibiotic prophylaxis. Trimethoprim-sulfamethoxazole or ciprofloxacin prophylaxis during the first 3 months after transplantation effectively reduces the frequency of UTIs to less than 10% and essentially eliminates urosepsis unless anatomic or functional derangement of the urinary tract is present.

Infections with multidrug-resistant microorganisms have recently emerged as an important cause of morbidity and mortality in organ transplantation. Hence, in some centers, the routine use of antibiotic prophylaxis is no longer recommended. Although strict aseptic surgical techniques and perioperative use of first-generation cephalosporins reduce the incidence of wound infections, infections are still observed, especially in subjects with comorbid conditions such as diabetes mellitus (DM) and obesity. Antibiotic-associated *Clostridium difficile* infection (particularly cephalosporins, ciprofloxacin, and amoxicillin-clavulanate) has become a serious epidemiologic problem worldwide. Judicious use of antibiotic prophylactic therapy may decrease the incidence of iatrogenic *C. difficile* infections. Whereas most infections during the first month are due to routine bacterial infections, nosocomial outbreaks have also been reported for rarer infections, such as *Legionella* from contaminated hospital water supplies.

Months 1 to 6

During months 1 to 6, opportunistic infections secondary to immunosuppression are most common. Viral infections, such as CMV, HSV, varicella-zoster virus (VZV), Epstein-Barr virus (EBV), HBV, and HCV, may occur from exogenous infection or reactivation of latent disease due to the immunosuppressed state. Repeated courses of antibiotics and corticosteroid therapy increase the risk of fungal infections, whereas viral infections may not only result from the immunosuppression but may themselves further impair immunity to increase the risk for additional opportunistic infections. Opportunistic infections may occur with *Pneumocystis jiroveci* (previously *Pneumocystis carinii*), *Aspergillus* species, *Listeria monocytogenes*, *Nocardia* species, and *Toxoplasma gondii*. Trimethoprim-sulfamethoxazole prophylaxis (see

Timetable of Infections*

Month 1 After Transplantation	Months 1–6	After 6 Months
Postoperative bacterial infections Urinary tract Respiratory Vascular access related Wound Intra-abdominal infections[1] Bacteremia **Nosocomial**, including *Legionella* species **Viral:** HSV, HBV, HCV, HIV **Fungal:** *Candida* **Organisms transmitted with donor organ** Untreated infection in recipient	**Opportunistic** or **unconventional infections** **Viral:** CMV, HHV-6, HHV-7, EBV, VZV, influenza, RSV, adenovirus **Fungal:** *Aspergillus* species, *Cryptococcus, Mucor* **Bacterial:** *Nocardia, Listeria, Mycobacterium* species *Legionella*, tuberculosis **Parasitic:** Pneumocystis, jiroveci, *Toxoplasma* and *Strongyloides* species, leishmaniasis	**Late opportunistic infections** *Cryptococcus*, CMV retinitis or colitis, VZV, parovirus-B-19, polyomavirus BK, *Listeria*, tuberculosis **Persistent infections:** HBV, HCV **Associated with malignancy** EBV, papillomavirus, HSV, HHV-8 **Community acquired** **Unusual sites** (e.g., paravertebral abscess)

Figure 101.1 Timetable of infections.* *Geographically focused infections will need to be considered in certain cases, such as malaria, leishmaniasis, trypanosomiasis, and strongyloidiasis. [1]Sources of infections specific to recipients of renal transplant: perinephric fluid collections (e.g., lymphoceles, wound hematomas, urine leaks), indwelling urinary stents, or anatomic or functional genitourinary tract abnormalities (e.g., ureteral stricture, vesicoureteric reflux, neurogenic bladder). CMV, cytomegalovirus; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HHV, human herpesvirus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; RSV, respiratory syncytial virus; VZV, varicella-zoster virus. *(Modified from reference 2.)*

Fig. 101.2 for trimethoprim-sulfamethoxazole allergy) eliminates or reduces the incidence of *Pneumocystis* pneumonia, *L. monocytogenes* meningitis, *Nocardia* species infection, and *T. gondii* infection.

After 6 Months

After 6 months, the infection risk can be categorized on the basis of the patient's status.

The first category consists of the majority of transplant recipients (70% to 80%), who have satisfactory or good allograft function, relatively low doses of immunosuppression medication, and no history of chronic viral infection. The risk of infection in these patients is similar to that of the general population, with community-acquired respiratory viruses constituting the major infective agents. Opportunistic infections are unusual unless environmental exposure has occurred.

The second group (approximately 10% of patients) consists of those with chronic viral infection that may include HBV, HCV, CMV, EBV, BK virus, or papillomavirus. In the setting of immunosuppression, such viral infections may lead to the development of progressive liver disease or cirrhosis (HBV, HCV), BK nephropathy, post-transplantation lymphoproliferative disease (EBV), or squamous cell carcinoma (papillomavirus).

The third group (approximately 10% of patients) consists of those who experience multiple episodes of rejection requiring repeated exposure to heavy immunosuppression. These patients are the most likely to develop chronic viral infections and superinfection with opportunistic organisms. Causative opportunistic pathogens include *P. jiroveci*, *L. monocytogenes*, *Nocardia asteroides*, and *Cryptococcus neoformans* and geographically restricted mycoses (coccidioidomycosis, histoplasmosis, blastomycosis, and paracoccidioidomycosis). In these high-risk candidates, lifelong prophylactic therapy with trimethoprim-sulfamethoxazole (80 mg/400 mg daily) has been advocated. Lifelong antifungal prophylaxis should also be considered and environmental exposure minimized (primarily avoidance of pigeons and areas of active building construction).

Newly Recognized Viral Infections

Several uncommon viral infections have recently been reported in both the early and late post-transplantation periods.[3] In the early post-transplantation period, outbreaks of donor-transmitted viral infections, such as lymphocytic choriomeningitis and West Nile virus, have been reported. Lymphocytic choriomeningitis occurs within the first 4 weeks after transplantation and is associated with a greater than 90% mortality rate.[3] In the late post-transplantation period, infections with community-acquired viral pathogens, including vaccine-preventable diseases such as mumps and measles, have reemerged. There is currently no effective antiviral therapy against either infection, and adherence to current guidelines for vaccinations in solid organ transplantation is recommended (discussed later). Other emerging or reemerging viral infections include adenovirus, human herpesvirus 6, metapneumovirus, parainfluenza, and respiratory syncytial virus. Interestingly, only rare cases due to severe acute respiratory syndrome (SARS) coronavirus have been reported.

The following sections discuss selected infections in renal transplant recipients. Suggested prophylactic therapy is shown in Figure 101.2.

Cytomegalovirus Infection

CMV infection may be a primary infection in a seronegative recipient (donor seropositive, recipient seronegative), reactivation of endogenous latent virus (donor seropositive or seronegative, recipient seropositive), or superinfection with a new virus strain in a seropositive recipient (donor seropositive, recipient seropositive). Primary CMV infection is usually more severe than reactive infection or superinfection.

CMV infection occurs primarily after the first month of transplantation and continues to be a significant cause of morbidity in the first 6 months after organ transplantation through both direct and indirect effects.

Clinical Manifestations

CMV infection may be asymptomatic, presenting as a mononucleosis-like syndrome or influenza-like illness with fever and leukopenia or thrombocytopenia, or a severe systemic disease. Hepatitis, esophagitis, gastroenteritis with colonic ulceration, pneumonia, chorioretinitis (associated with retinal hemorrhage), and even otitis[4] may occur. In enterically drained pancreas transplantation, CMV has been reported to cause bleeding ulcer from the duodenal segment. Clinical manifestations usually

Suggested Prophylactic Therapy for Recipients of Renal Transplants

	Comments
Trimethoprim-sulfamethoxazole (TMP–SMZ)* (80/400 mg) one tablet daily × 3 months	Its routine use reduces or eliminates the incidence of *Pneumocystis jiroveci, Listeria monocytogenes, Nocardia asteroides,* and *Toxoplasma gondii* In renal transplant recipients, TMP–SMZ reduces the incidence of urinary tract infection from 30%–80% to <5%–10%
Monthly intravenous or aerosolized pentamidine > dapsone† > or atovaquone‡	Replaces TMP–SMZ for patients with sulfa allergies
Nystatin 100,000 units/ml, 4 ml after meals and before bedtime *or* Fluconazole§ 200 mg one tablet daily × 2 months	For fungal prophylaxis Close monitoring of cyclosporine or tacrolimus levels when starting and stopping antifungal agents
Acyclovir/valganciclovir/ganciclovir	For CMV prophylaxis, see Figure 101.3

Figure 101.2 Suggested prophylactic therapy for recipients of renal transplants. *Prophylactic therapy for the first 3 months after transplantation is generally recommended. For patients receiving sirolimus immunosuppression, 1 year of therapy is recommended. †Check glucose-6-phosphate dehydrogenase deficiency before initiation of therapy. ‡In order of efficacy. §Fluconazole is recommended for recipients of combined kidney-pancreas or combined kidney-liver transplants.

Consider reinstitution of prophylactic therapy for 3 months after acute rejection episodes requiring intensification of immunosuppression. CMV, cytomegalovirus.

occur 1 to 4 months after transplantation except for chorioretinitis, which occurs later in the transplant course.[5] Quantitative CMV assays of serum in patients with invasive colitis and gastritis or neurologic disease including chorioretinitis are often negative. Diagnosis in such cases may require invasive testing and biopsies.

Immunomodulating Effects of CMV Infection

CMV infection is associated with immune modulation and dysregulation of helper/suppressor T cells and may be a risk factor for chronic allograft rejection, secondary infection with opportunistic agents (such as *P. jiroveci*, *Candida*, and *Aspergillus*), reactivation of human herpesvirus HHV-6 and HHV-7, and the development of post-transplantation lymphoproliferative disease. CMV infection is also associated with acceleration of HCV infection and the development of new-onset DM after transplantation.[6]

Risk Factors for CMV Infection

Donor and recipient seropositive status and the use of blood products from a CMV-seropositive donor are well-established risk factors for CMV infection. Other factors associated with an increased risk of CMV infection include the use of antilymphocyte antibodies, prolonged or repeated course of antilymphocyte preparations, comorbid illnesses, neutropenia, and acute rejection episodes. Mycophenolate mofetil (MMF) has been reported to increase the risk for CMV viremia and CMV disease in some studies, especially in patients receiving more than 3 g/day. Although the cause-effect of allograft rejection and CMV infection remains conjectural, several studies suggest that one may increase the risk for the other, possibly owing to the release of inflammatory cytokines. Prevention of CMV infection, for example, results in a lower incidence of graft rejection.[7]

Prevention and Treatment

Prophylactic therapy begins in the immediate postoperative period. Preemptive therapy involves treatment of those who are found to seroconvert by quantitative laboratory assays of the blood, such as CMV DNA polymerase chain reaction (PCR) or pp65 antigenemia during surveillance studies. The former assay is highly specific and sensitive for the detection of CMV viremia. The latter is a semiquantitative fluorescent assay in which circulating neutrophils are stained for nonspecific uptake of CMV early antigen (pp65).

Various prophylactic and preemptive protocols have been developed. Oral acyclovir provides effective CMV prophylaxis solely in recipients of seronegative donor organs. Oral or intravenous ganciclovir or oral valganciclovir provides superior prophylactic or preemptive therapy against primary CMV infection or CMV reactivation. Prophylactic or preemptive therapy should be based on the intensity of immunosuppression (i.e., during antilymphocyte antibody therapy) and the seropositive status of the donor, the recipient, or both. Seronegative individuals who receive organs from latently infected seropositive donors are at greatest risk for primary infection and severe CMV disease. A suggested CMV prophylaxis protocol is shown in Figure 101.3.

Clinical CMV disease is treated with intravenous ganciclovir (5 mg/kg twice daily for 3 weeks, dose adjusted for renal dysfunction) with reduction of immunosuppression, such as withholding of MMF. Treatment is continued until clearance of viremia as assessed by PCR or antigenemia. Anecdotal reports have suggested that calcineurin inhibitor (CNI) to sirolimus switch in conjunction with ganciclovir therapy may be beneficial in patients with apparent ganciclovir-resistant CMV.[8]

In patients with gastrointestinal CMV infection, the use of these assays is unreliable, and repeated endoscopy should be considered to assess response to therapy. In patients who have primary infection and respond slowly to therapy, the addition of CMV hyperimmune globulin (150 mg/kg per dose given intravenously every 3 to 4 weeks for 3 months) may be of benefit.[5] In patients with tissue invasive disease, intravenous ganciclovir is recommended with conversion to oral therapy when there is evidence of a good response, followed by a 3-month course of oral ganciclovir or valganciclovir prophylaxis.[5] Whereas oral valganciclovir provides good bioavailability and may be effective in mild CMV disease, it is not recommended for the treatment of

Suggested Cytomegalovirus Prophylaxis Protocol[1]

For CMV– recipients of a CMV– organ
Acyclovir 400 mg daily (or valganciclovir 450 mg daily) × 3 months
CMV DNA every 2 weeks × 3 months

For CMV– recipients of a CMV+ organ
During antibody treatment, DHPG[2] 5.0 mg/kg IV everyday, then following antibody treatment/valganciclovir 900 mg PO everyday × 6 months
If no antibody treatment: valganciclovir 900 mg everyday for 6 months
CMV DNA every 2 weeks x 3 months

For CMV+ recipients of a CMV– organ
During antibody treatment, DHPG 5.0 mg/kg IV everyday, then following antibody treatment, valganciclovir 900 mg PO everyday × 6 months
If no antibody treatment: acyclovir 400 mg daily (or valganciclovir 450 mg daily) × 3 months
CMV DNA every 2 weeks × 3 months

For CMV+ recipients of a CMV+ organ
During antibody treatment, DHPG 5.0 mg/kg IV everyday, then following antibody treatment, valganciclovir 900 mg PO everyday × 6 months
If no antibody treatment: acyclovir 400 mg daily (or valganciclovir 450 mg daily)[3] × 3 months
CMV DNA every 2 weeks × 3 months

Figure 101.3 Suggested cytomegalovirus prophylaxis protocol. [1]If CMV status is unknown, give intravenous DHPG until CMV status is determined. [2]Dose adjustment for renal function is necessary. DHPG, 9-(1,3-dihydroxy-2-propoxymethyl) guanine. [3]Although low-dose valganciclovir, 450 mg daily, has been shown to be effective, the Canadian Society of Transplantation Consensus Workshop on CMV management recommends dosing valganciclovir at 900 mg daily for CMV+ recipients of a CMV+ organ (kidney, liver, pancreas, heart). *(From reference 9.)*

established CMV disease, and intravenous ganciclovir is required. Cidofovir and foscarnet are alternative therapeutic agents, but in view of their nephrotoxicity and potential synergistic nephrotoxicity with CNIs, they are reserved for use when ganciclovir-resistant strains are clinically suspected.

Candida Infections

Candida infections are common in transplant recipients; *Candida albicans* and *Candida tropicalis* account for 90% of the infections. DM, high-dose corticosteroids, and broad-spectrum antibacterial therapy predispose patients to mucocutaneous candidal infections such as oral candidiasis, intertriginous candidal infections, esophagitis, vaginitis, and UTI. Skin infections are treated with nystatin and topical clotrimazole; candidal UTIs are treated with fluconazole or voriconazole or more rarely with liposomal amphotericin or caspofungin for fluconazole-resistant species (see Chapter 53). Whenever possible, foreign objects such as bladder catheters, surgical drains (e.g., percutaneous nephrostomy tube), and urinary stents should be promptly removed. The ideal management of asymptomatic candiduria in immunocompromised patients remains uncertain (see Chapter 53), but a short course (7 to 10 days) of fluconazole is generally recommended. Systemic antifungal therapy is indicated in the presence of any positive blood culture for *Candida* species.

BK Infection

BK virus is a ubiquitous human virus with a peak incidence of primary infection in children 2 to 5 years of age and a seroprevalence rate of more than 60% to 90% among the adult population worldwide. After primary infection, BK virus preferentially establishes latency within the genitourinary tract and frequently is reactivated in the setting of immunosuppression. In renal transplant recipients, BK virus is associated with a range of clinical syndromes including asymptomatic viruria with or without viremia, ureteral stenosis and obstruction, interstitial nephritis, and BK allograft nephropathy. During the last decade, BK nephropathy has emerged as an important cause of allograft dysfunction after renal transplantation. Most series report that 30% to 40% of renal transplant recipients develop BK viruria, 10% to 20% develop BK viremia, and 2% to 5% develop BK nephropathy. The highest prevalence of BK viruria and viremia occurs at 2 to 3 months and 3 to 6 months, respectively. The risk for development of BK viremia increases when urine viral load is greater than 10^4 copies/ml, whereas BK nephropathy is unusual in the absence of BK viremia. BK nephropathy commonly presents with an asymptomatic rise in serum creatinine during the first post-transplantation year. However, BK nephropathy may occur as early as the first week to as late as 6 years after transplantation. Diagnosis is made by allograft biopsy, which demonstrates BK viral inclusions in renal tubular cell nuclei and occasionally in glomerular parietal epithelium (Fig. 101.4A). There are variable degrees of interstitial mononuclear inflammation (Fig. 101.4B), often with plasma cells, degenerative changes in tubules, and focal tubulitis, which may mimic acute rejection. BK nephropathy often is associated with very focal and sharply demarcated areas of tubulointerstitial inflammation, corresponding to foci of viral infection. Immunohistochemistry (Fig. 101.4C), *in situ* hybridization, or electron microscopy is required to confirm the diagnosis. BK infection and acute rejection may occur simultaneously, and distinguishing between BK nephropathy and acute rejection or the presence of both can be a diagnostic challenge. In late BK nephropathy, few characteristic intranuclear inclusions are seen, and the histologic changes may be indistinguishable from chronic rejection. A histologic classification system for BK nephropathy based on the degree of active inflammation, acute tubular injury, and tubulointerstitial scarring may have prognostic significance.[10] Urine cytology for decoy cells and quantitative determinations of viruria and of viral load in blood have been proposed as surrogate markers for the diagnosis of BK nephropathy.

Treatment strategies include reduction in immunosuppression that involves reduction or discontinuation of MMF and azathioprine with judicious reduction in CNI therapy or other immunosuppressive regimen. Switching from tacrolimus to cyclosporine or to sirolimus (rapamycin) has resulted in resolution of BK nephropathy and viremia or viruria in anecdotal case reports. Switching from CNI to sirolimus may have the added benefit of avoiding the long-term nephrotoxic effect of CNI therapy. Although no approved antiviral drug is available, adjunctive therapy with leflunomide, cidofovir, quinolones, or intravenous immune globulin (IVIG) may be beneficial, especially in patients with progressive allograft dysfunction. Quinolones are preferred by some centers because of low cost and ease of administration; leflunomide is used by others because of its potential simultaneous antiviral and immunosuppressive properties. Cidofovir is highly concentrated in urine and renal tissue, and the use of low-dose cidofovir in BK nephropathy has been reported to be devoid of nephrotoxicity or serious adverse events. Anecdotal

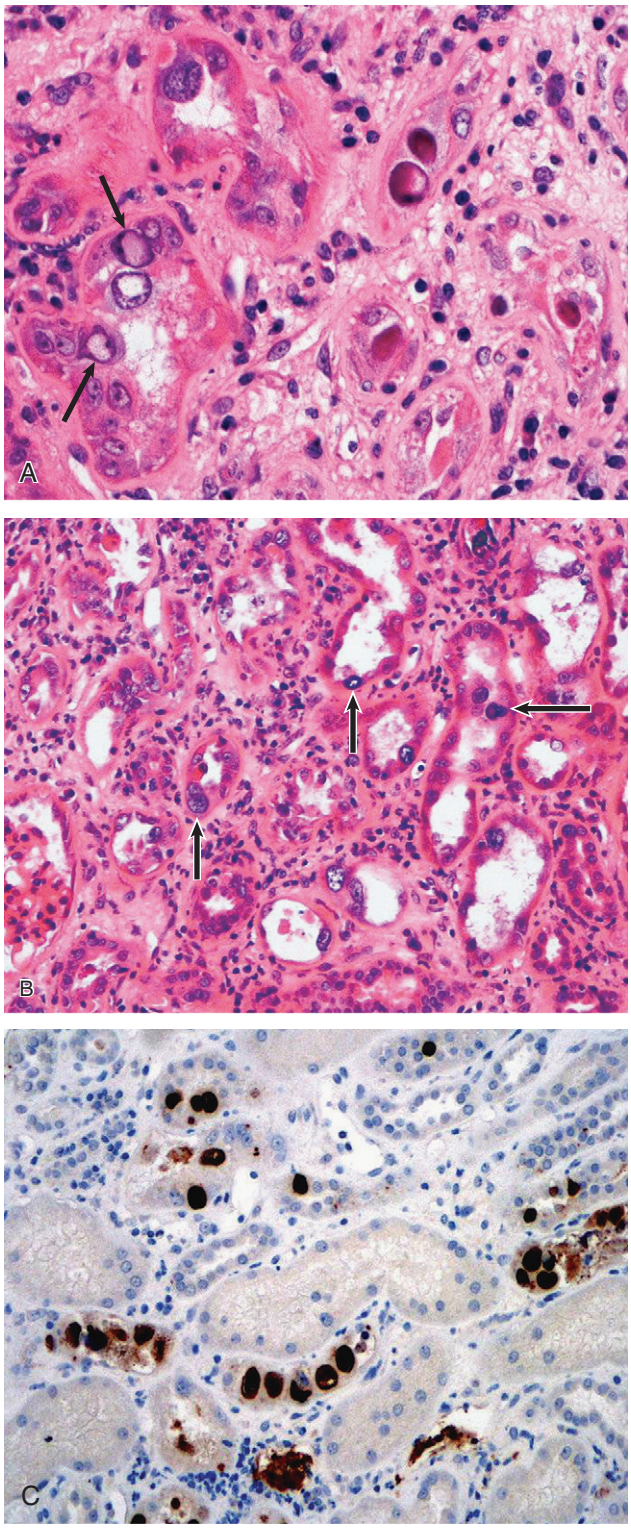

Figure 101.4 BK virus nephropathy. A, Prominent intranuclear viral inclusions are present within tubular epithelial cells *(arrows)*. (Hematoxylin and eosin; original magnification ×400.) **B,** Tubulointerstitial nephritis with diffuse intranuclear *Polyomavirus* inclusions *(arrows)*. (Hematoxylin and eosin; original magnification ×200). **C,** Immunohistochemistry staining highlights intranuclear *Polyomavirus* inclusions. (SV40 immunoperoxidase stain; original magnification ×200.) *(Courtesy Charles Lassman and William Dean Wallace, David Geffen School of Medicine at UCLA, Los Angeles, California, USA.)*

reports have suggested that IVIG may be effective in treating corticosteroid-resistant rejection,[11] and its use may be beneficial in patients with concomitant rejection and BK nephropathy or in those with histopathologic changes that are indistinguishable from those of rejection.

Despite treatment, 30% to more than 60% of patients with established BK nephropathy developed progressive decline in renal function with graft loss. Early diagnosis and intervention may improve prognosis. Intensive monitoring of urine and serum for BK by PCR during the first year with preemptive reduction of immunosuppressive therapy may lead to the resolution of viremia and prevent BK nephropathy. In the absence of active viral replication, patients with graft loss due to BK nephropathy can safely undergo retransplantation. Active surveillance for BK virus reactivation after transplantation is recommended. Suggested guidelines for post-transplantation screening and monitoring for BK replication are shown in Figure 101.5.

Other Infections

Tuberculosis (TB) infection in the renal transplant recipient varies according to the prevalence in the general population (e.g., the incidence of TB in transplant recipients has been reported to occur in 0% to 1.3% in the United States, compared with 11% in South Africa and 11% to 14% in India and Pakistan).[12] Most TB infection in the transplant recipient results from reactivation of dormant lesions in the setting of immunosuppressive therapy. Hence, all renal transplant candidates should have a PPD skin test (tuberculin skin test) placed before transplantation. A positive skin test response or a prior history of TB mandates further evaluation to rule out active disease. Isoniazid prophylaxis for a total of 9 months is recommended for those who have a positive skin test response. Of interest, most of the patients who develop TB after transplantation had negative PPD skin test results before transplantation.[13] Some centers recommend isoniazid prophylactic therapy in selected PPD-negative patients with (1) a history of inadequately treated TB, (2) radiographic evidence of granulomatous disease and no history of adequate treatment, (3) an organ from a PPD-positive donor, or (4) close and prolonged contact with a case of active TB.[13] In patients with a known history of adequately treated TB infection, we advocate the use of isoniazid prophylaxis for the first 9 months after transplantation and during intensification of immunosuppression. Others, however, have suggested that isoniazid prophylaxis is not indicated for those patients whose TB had been properly treated.[12] Clinical, radiologic, or culture evidence of active TB infection is a contraindication to transplantation. Enzyme-linked immunospot (ELISPOT), which detects T cells specific for *Mycobacterium tuberculosis* antigens, is unaffected by bacille Calmette-Guérin (BCG) vaccination and has become a major advance in TB screening. In some centers, the tuberculin skin test has been replaced by the ELISPOT assays (T-SPOT.TB assay).

A rare but important cause of infection in transplant patients, particularly those from endemic areas such as Southeast Asia, is *Strongyloides*. In the presence of immunosuppression, a "hyperinfection" syndrome may be observed with parasitic pneumonia (Fig. 101.6) and gastrointestinal involvement.

GASTROINTESTINAL DISEASE

Post-transplantation gastrointestinal complications are common and can arise from a variety of causes. Only selected complications are discussed; for a comprehensive review of

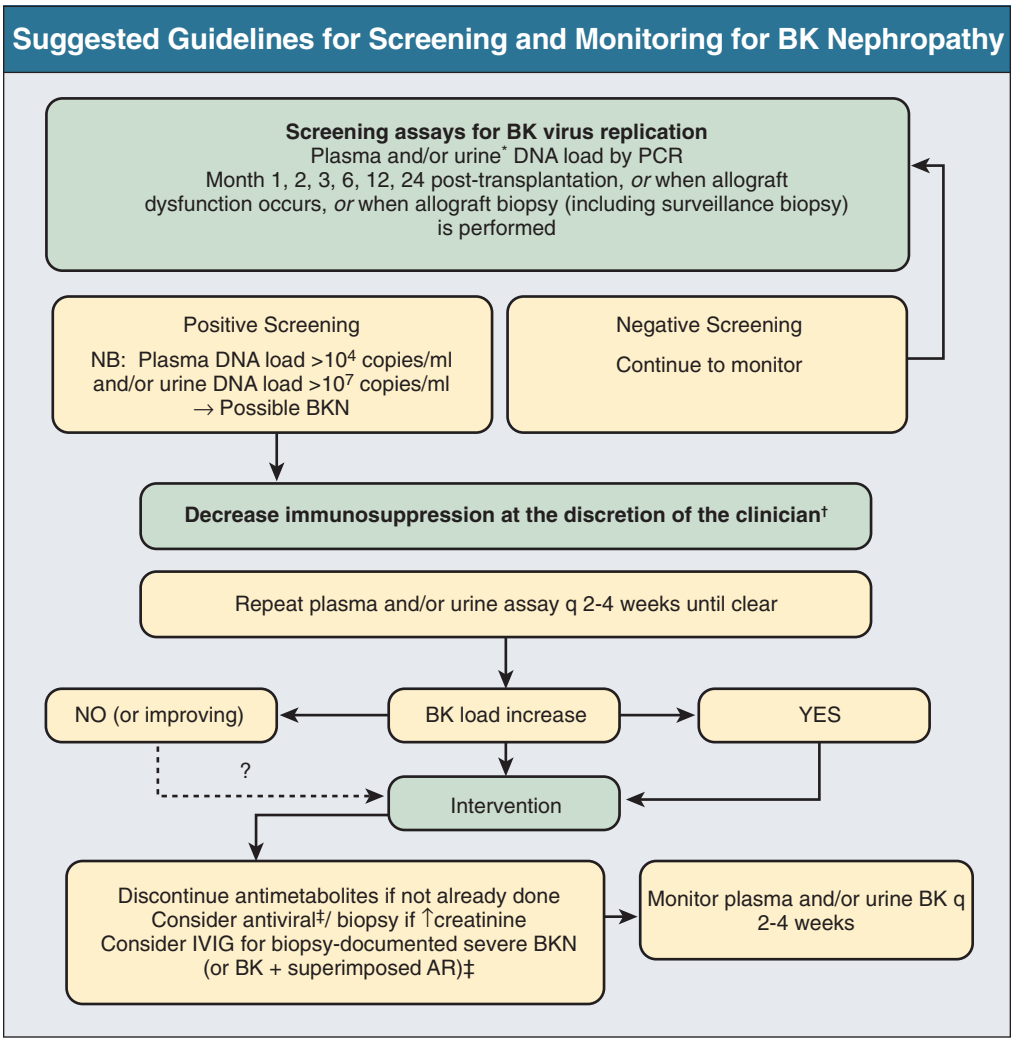

Figure 101.5 Guidelines for screening and monitoring for BK nephropathy. *Institution dependent. †Preemptive immunosuppression reduction may be associated with resolution of viruria or viremia and ↓ incidence of BK nephropathy. ‡See text. AR, acute rejection; BKN, BK nephropathy; IVIG, intravenous immune globulin; NB: note well; PCR, polymerase chain reaction.

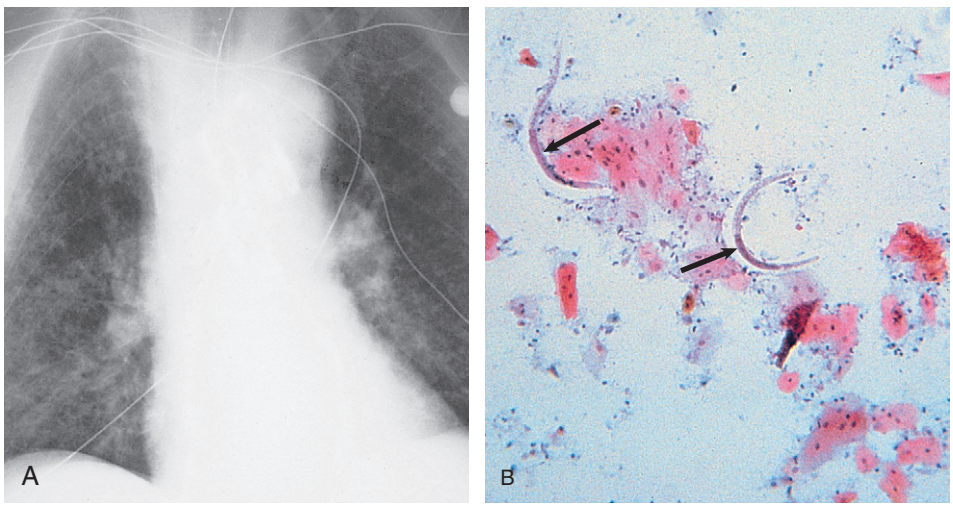

Figure 101.6 Disseminated strongyloidiasis in an immunocompromised patient. A, Chest radiograph showing a diffuse bilateral interstitial process. **B,** Gram stain of sputum shows filariform larvae of *Strongyloides stercoralis (arrows). (Courtesy R. Johnson, University of Colorado, Denver, Colorado, USA.)*

post-transplantation gastrointestinal complications, readers are referred to Chapter 83 and references 13 and 14.

Drug-Related Gastrointestinal Complications

MMF commonly causes gastrointestinal side effects, including nausea, vomiting, dyspepsia, anorexia, flatulence, and diarrhea. Dose reduction, transient discontinuation of the drug, or dividing the dose into three or four times a day often ameliorates or resolves the symptoms. Switching to the enteric-coated formulation of MMF may improve gastrointestinal tolerability in some patients but has not been consistently shown to be better than the original formulation. A large randomized double-blind study using patient-reported outcomes to assess the impact of gastrointestinal symptoms on patients' health-related quality of life and symptom burden is currently under way. Sirolimus may cause oral mucocutaneous lesions that can be confused with HSV or CMV infection but are culture negative. Drug-related oral ulcers usually resolve after discontinuation of the offending agent. Sirolimus, tacrolimus, and cyclosporine have also been suggested to cause diarrhea in some patients.

Infections

Post-transplantation infections of the gastrointestinal tract may be viral, fungal, or bacterial in etiology. Viral infections are most commonly caused by CMV and HSV; *C. albicans* and *C. tropicalis* are common opportunistic fungal infections. Leukoplakia and post-transplantation lymphoproliferative disorder (PTLD) may develop in patients with EBV infection (PTLD is discussed in a later section). Commonly encountered bacterial pathogens include *Clostridium difficile* and *Helicobacter pylori*.

Cytomegalovirus Infection

CMV can affect any segment of the gastrointestinal tract. Patients may present with dysphagia, odynophagia, nausea, vomiting, gastroparesis, abdominal pain, diarrhea, or gastrointestinal bleeding. Leukopenia and elevated transaminases are common. Persistent or unexplained symptoms of nausea, vomiting, or diarrhea, particularly in the early post-transplantation period or during intensification of immunosuppression, warrant further investigation with upper or lower endoscopies and biopsies.

Herpes Simplex Virus Infection

HSV infection results primarily from reactivation of endogenous latent virus, causing clinical infection within the first 1 to 2 months after transplantation. Patients commonly present with oral mucocutaneous lesions or gingivostomatitis with or without odynophagia and dysphagia. HSV esophagitis has been noted to occur in patients receiving high-dose corticosteroids and antilymphocyte preparations for acute rejection. Limited oral mucocutaneous lesions are treated with oral acyclovir; extensive infections require intravenous acyclovir or ganciclovir. Rare cases of HSV hepatitis have been reported.[14] The routine use of acyclovir prophylaxis in the early post-transplantation period is recommended.

Fungal Infections

Candida stomatitis and esophagitis are common during the first 6 months after transplantation and are increased in subjects with leukopenia or with severe immunosuppression, diabetes, or concomitant infections. Bleeding or perforation with formation of tracheoesophageal fistulas has been reported. Prophylactic oral nystatin "swish and swallow" during the first month after transplantation is recommended. In high-risk candidates, including liver or pancreas transplant recipients and those receiving antilymphocyte antibody therapy, fluconazole prophylactic therapy (3 to 6 months) is warranted.

Clostridium Infection

Clostridium difficile infection may be asymptomatic or present with diarrhea, intestinal obstruction, or even fulminant pseudomembranous colitis with toxic megacolon and perforation. *C. difficile* colitis is reported in 3.5% to 16% of transplant recipients.[15] Risk factors include young (<5 years) or advanced age, female gender, use of monoclonal antibodies to treat acute rejection episodes, and intra-abdominal graft placement. Among transplant recipients receiving antimicrobial therapy, *C. difficile*–associated diarrhea develops in approximately 50% of patients.[15] In mild cases of *C. difficile* infection, oral metronidazole is as effective as oral vancomycin and is the preferred first-line treatment. Treatment failure, however, requires treatment with oral vancomycin. In severely ill patients with gastrointestinal dysmotility or ileus, in which oral agents may not reach the colonic mucosa, metronidazole should be administered intravenously. Severe colonic disease refractory to medical treatment may necessitate colectomy.

Helicobacter Infection

Helicobacter pylori infection is associated with a wide range of gastrointestinal complications including chronic gastritis, duodenal and gastric ulcers, mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric carcinoma, both in the general population and in recipients of solid organ transplants. Treatment includes a triple-drug regimen consisting of two antibiotics and an acid-suppressive agent such as an H_2 blocker or a proton pump inhibitor. The first-line *H. pylori* regimen as recommended by the American College of Gastroenterology is shown in Figure 101.7. In recipients of orthotopic heart transplants, triple-drug therapy resulted in a lower eradication rate compared with the general population, suggesting that immunosuppression may hinder the clearance of *H. pylori*. Unexplained dyspeptic or reflux symptoms should be investigated further with endoscopy and biopsy to exclude malignant transformation. *H. pylori* is now recognized as a risk factor for MALT lymphoma, which may occur in kidney, liver, and heart transplant recipients. In renal transplant recipients infected with *H. pylori*, MALT lymphoma may be less aggressive than other lymphomas, and the disorder may be cured by eradication of *H. pylori*.

Colon Disorders

Post-transplantation colonic complications, such as diverticulitis and colonic perforation, may be life-threatening and difficult to diagnose because symptoms may be masked by immunosuppressive therapy, particularly in the early postoperative period. Diverticulitis complicated by perforation, abscess formation, phlegmon, or fistula has been reported to occur in 1.1% of renal transplant recipients[16] and may be increased in patients with polycystic kidney disease (PKD).

Early post-transplantation colonic perforations are largely due to high-dose corticosteroids, diverticulitis, CMV colitis, and intestinal ischemia; perforations occurring late or years after transplantation are commonly due to diverticulosis or malignant disease. Abdominal symptoms may be absent because of the effects of immunosuppression and may only be suggested by the

First-Line Treatment Regimens for *Helicobacter pylori* as Recommended by the American College of Gastroenterology

Penicillin allergies	
No*	Standard-dose PPI twice daily (or esomeprazole once daily) + clarithromycin 500 mg twice daily + amoxicillin 1000 mg twice daily for 10–14 days
Yes†	Standard–dose PPI twice daily + clarithromycin 500 mg twice daily + metronidazole 500 mg twice daily for 10–14 days
Yes	Bismuth subsalicylate 525 mg orally 4 times daily + metronidazole 250 mg orally 4 times daily + tetracycline 500 mg orally four times daily + ranitidine 150 mg orally twice daily (or standard-dose PPI once daily to twice daily) for 10–14 days

Figure 101.7 First-line treatment regimens for *Helicobacter pylori* as recommended by the American College of Gastroenterology. *For patients who have not previously received a macrolide antibiotic. †For patients who have not previously received a macrolide antibiotic or who are intolerant of bismuth quadruple therapy. PPI, proton pump inhibitor.

presence of tachypnea and tachycardia. Mortality after colonic perforation is high. Management includes prompt exterioration of the perforated colon, early and broad-spectrum antimicrobial therapy, and minimization of immunosuppressive therapy. Although uncommon, the presence of abdominal pain and gastrointestinal bleeding with unexplained fevers or weight loss should raise the suspicion for gastrointestinal TB. The characteristic endoscopic findings include circular ulcers, small diverticula, and sessile polyps. The presence of caseating granulomas or acid-fast bacilli, or both, confirms the diagnosis.

Immunizations Before and After Transplantation

All potential renal transplant candidates should receive immunization for hepatitis B, pneumococcus, and other standard immunizations appropriate for age. Up-to-date recommendations for routine adult immunizations are available through the Centers for Disease Control and Prevention website *(www.cdc.gov/nip/rec/adult-schedule.pdf)*. Immunizations should ideally be administered at least 4 to 6 weeks before transplantation to achieve optimal immune response and to minimize the possibility of live vaccine–derived infection in the post-transplantation period. Household members, close contacts, and health care workers should also be fully immunized.

Live virus or live organism vaccines should be avoided after transplantation. These include measles-mumps-rubella (MMR), live oral poliovirus (which is also contraindicated for household contacts), smallpox (vaccinia), varicella, yellow fever, adenovirus, live oral typhoid (Ty21a), BCG, and intranasal influenza vaccine. In addition, exposure to persons who have chickenpox or herpes zoster should be avoided until the lesions have crusted over and no new lesions are appearing. Vaccinations using inactivated or killed microorganisms, components, and recombinant moieties are safe for transplant recipients. These include hepatitis A and hepatitis B, intramuscular influenza A and B, pneumococcal, *Haemophilus influenzae* b, inactivated poliovirus vaccine, diphtheria-pertussis-tetanus (DPT), and *Neisseria meningitidis*.

In general, vaccination should be avoided in the first 6 months after transplantation because of the potential for stimulating the immune response, with a higher chance of graft dysfunction and rejection. In addition, vaccinations within the first 6 months after transplantation are often ineffective because of heavy immunosuppression. For prevention of infection in adult travelers after solid organ transplantation, readers are referred to reference 17. Recommended vaccinations before and after transplantation are listed in Figure 101.8.

Recommended Immunizations Before and After Transplantation

Vaccine	Pre	Post
Measles–mumps–rubella	X	–
Diphtheria–tetanus-pertussis	X	Diphtheria and tetanus[a]
Varicella	X	Controversial
Poliovirus	X	Inactivated polio virus vaccine[b]
Haemophilus influenzae b	X	X
Influenza	X	X[c]
Pneumococcus	X	X[d]
Hepatitis B	X	X[e]
Hepatitis A	X	X[f]
Human papillomavirus (HPV)	X[g]	–

Figure 101.8 Recommended immunizations before and after transplantation. [a]Booster every 10 years. [b]For travelers to endemic areas (i.e., some parts of Asia, Africa). [c]Annually. [d]Every 3 to 5 years. [e]Monitor titers. [f]For travelers to endemic areas. [g]Nonpregnant female transplant candidates aged 9 to 26 years.

TRANSPLANT-ASSOCIATED MALIGNANT NEOPLASMS

Recipients of organ transplants are at increased risk for development of neoplasms compared with the general population. Similar to post-transplantation infectious complications, the time to occurrence of different types of malignant neoplasms after transplantation appears to follow a timetable pattern. The Israel Penn International Transplant Tumor Registry data on the time of appearance of different neoplasms after solid organ transplantation are shown in Figure 101.9. PTLD generally occurs early after transplantation; skin cancers occur with increasing frequency with time. The intensity and duration of immunosuppression as well as the ability of these agents to promote replication of various oncogenic viruses are important risk factors. The associations between human papillomaviruses and cervical and vulvar carcinoma, EBV and PTLD, HBV and HCV and hepatocellular carcinoma, and HHV-8 and Kaposi's sarcoma are well established. Figure 101.10 provides a summary

Time of Appearance of Neoplasms After Transplantation and Initiation of Immunosuppression

Type of Cancer	Median (months)
Lymphomas	12
Kaposi's sarcoma	13
Carcinomas (excluding Kaposi's)	41
Carcinomas of cervix	46
Hepatobiliary carcinomas	68
Skin cancers	69
Carcinoma of vulva or perineum	114
All cancers	46

Figure 101.9 Time of appearance of neoplasms after transplantation and initiation of immunosuppression.

Meta-Analysis Standardized Incidence Ratios for Cancers Related to Infections in Transplant Recipients

Cancers	Meta-Analysis SIRs
EBV-related cancers	
Hodgkin's lymphoma	3.89 (2.42–6.26)
Non-Hodgkins lymphoma	8.07 (6.40–10.2)
HHV–8–related cancers	
Kaposi 's sarcoma	208.0 (114–369)
HBV/HCV-related cancers	
Liver	2.13 (1.16–3.91)
HPV-related cancers	
Cervix uteri	2.13 (1.37–3.30)
Vulva and vagina	22.8 (15.8–32.7)
Penis	15.8 (5.79–34.4)
Anus	4.85 (1.36–17.3)
Oral cavity and pharynx	3.23 (2.40–4.35)
Non-melanocytic–related skin	28.6 (9.39–87.2)

Figure 101.10 Meta-analysis standardized incidence ratios (SIRs) for cancers related to infections in transplant recipients. EBV, Epstein-Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HHV, human herpesvirus; HPV, human papillomavirus. *(Modified from reference 18.)*

of the incidence of cancers related to infections in transplant recipients.[18]

An analysis of the USRDS database[19] documented that the cancer rates for most common cancers, such as colon, lung, prostate, stomach, esophagus, pancreas, ovary, and breast, are nearly twofold higher after kidney transplantation compared with the general population. Although registry studies have limitations, all transplant recipients should adhere to standard cancer surveillance appropriate for age (Fig. 101.11).[20] In patients with a history of pre-transplantation malignant neoplasms, close monitoring for recurrences in the post-transplantation period is mandatory. The highest recurrence rates have been observed with multiple myeloma (67%), non-melanoma skin cancers (53%), bladder carcinomas (29%), sarcomas (29%), symptomatic renal cell carcinomas (27%), and breast carcinomas (23%).[21] In an analysis of registry data involving 90 patients with a history of pretransplantation prostate adenocarcinoma (77 renal, 10 heart, and 3 liver transplant recipients), prostate cancer recurrences were found to relate to the stage of disease at initial diagnosis.[22] Tumor recurrence rates were 14%, 16%, and 33% for stage I, stage II, and stage III diseases, respectively. Hence, a longer waiting time may be necessary for more advanced disease. Suggested guidelines for tumor-free waiting periods for common pretransplantation malignant neoplasms are shown in Figure 101.12.

Post-Transplantation Lymphoproliferative Disorder

PTLD is the most common post-transplantation malignant neoplasm in children; in adults, it is the second most common malignant neoplasm after skin cancer. PTLD has been reported to occur in 1% to 5% of renal transplant recipients.

The majority of PTLD is non-Hodgkin's lymphoma of B-cell origin, and more than 80% to 90% are linked to EBV infection. Based on the World Health Organization classification, PTLD can be divided into three distinct morphologic groups: (1) diffuse B-cell hyperplasia, (2) polymorphic PTLD (usually monoclonal), and (3) monomorphic PTLD that includes high-grade invasive lymphoma of B- or T-lymphocyte centroblasts. Diffuse B-cell hyperplasia is usually seen in children and young adults and commonly occurs within the first year after transplantation. Polymorphic PTLD represents the most common type of PTLD in both children and adults and may occur at any time after transplantation. In contrast, monomorphic B-cell PTLD is often seen several years after transplantation and may resemble non-Hodgkin's lymphoma in the general population. In a retrospective analysis of registry data for 402 recipients of kidney transplants, PTLD occurred at a median of 18 months (range, 1 to 310 months) after transplantation.

PTLD may present with constitutional symptoms such as fevers, night sweats, and weight loss or localized symptoms of the respiratory tract (infection or mass, including tonsillar or even gingival involvement), gastrointestinal tract (diarrhea, pain, perforation, bleeding, mass), or central nervous system (CNS) (headache, seizure, confusion). In contrast to lymphomas in the general population, in which lymph nodes are almost always involved, lymph node involvement is absent in more than 80% of patients with PTLD.

Risk factors for PTLD include primary EBV infection, younger age, antecedent history of CMV disease, and use of antilymphocyte antibody (e.g., antithymocyte globulin, OKT3). A history of pretransplantation malignant disease and fewer HLA matches are associated with an increased risk of PTLD. Cyclosporine and tacrolimus may enhance the development of EBV-associated PTLD by directly promoting the survival of EBV-infected B cells, presumably through the inhibition of EBV-transformed cells from apoptosis.[23]

Reduction or discontinuation of immunosuppressive therapy, particularly antilymphocyte antibody, cyclosporine, tacrolimus, or MMF, is recommended as first-line treatment; prednisone is increased to 10 to 15 mg daily to prevent allograft rejection. Sirolimus has a strong antiproliferative effect on PTLD-derived B-cell lines,[24] but whether sirolimus may limit B-cell lymphoma growth while simultaneously providing immunosuppression to prevent graft rejection awaits studies. Acyclovir or ganciclovir therapy and reduction in immunosuppression are beneficial and may be curative in benign polyclonal B-cell proliferation. The

Preventive Care Recommendations for Cancer Surveillance in Renal Transplant Recipients

Screening For	Starting at Age	Preventive Care	Screening Frequency
Colorectal cancer	Average risk: 50 years	Colonoscopy or FOBT + Flex sig[1]	Colonoscopy: every 10 years FOBT[1]: every year Flex sig[1]: every 5 years
	Increased risk: 40 years	Colonoscopy	Every 5 years if a parent or sibling had colorectal cancer at <60 years of age
		or	At 10 years younger than the youngest family member with cancer
		or	Every 10 years if the relative was 60 years
		or	Consider referral to medical genetics if two or more first degree relatives had colorectal cancer
Skin cancer[1]	Monthly self examination of skin, total-body skin examination every 6 to 12 months by qualified physicians and dermatologists[2]		
Females			
Breast cancer	50–69[1] years	Breast examination and screening mammography	Every 1 or 2 years
	40–49[1] years	Breast examination and screening mammography	Every 1 or 2 years (no evidence for or against for this age group)
	Before age 30 years (if mother or sister had breast cancer)		
Cervical cancer	Once sexually active	Pap smear and pelvic examination	Every year
Males			
Prostate cancer	50 years	Digital rectal examination	Every year
	40[3] years	PSA testing	Frequency for testing is not established

Figure 101.11 Preventive care recommendations for cancer surveillance in renal transplant recipients. [1]As recommended by the American Transplant Society and the European Best Practice Guidelines on renal transplantation. [2]The American College of Preventive Medicine recommends regular screening for high-risk individuals but none for low-risk individuals. [3]Recommended for African Americans, family history of prostate cancer, patients receiving chronic immunosuppression for organ transplantation. FOBT, fecal occult blood testing; Flex sig, flexible sigmoidoscopy; PSA, prostate-specific antigen. *(Sources: The 2001 Cleveland Clinic Foundation Cancer Surveillance Task Force and reference 20.)*

role of antiviral therapy in B-cell monoclonal malignant transformation is less well defined; 50% to 90% mortality has been reported despite antiviral therapy. Surgical resection with or without adjunctive local irradiation has been suggested for localized disease. Local irradiation has been advocated as the treatment of choice for PTLD involving the central nervous system.

In lesions not amenable to surgery or more aggressive monoclonal types of PTLD, chemotherapy has been used with favorable results compared with reduction in immunosuppression alone. The most frequently used regimens are CHOP (cyclophosphamide, doxorubicin [Adriamycin], vincristine, and prednisone) and VAPEC-B (doxorubicin, etoposide, cyclophosphamide, methotrexate, bleomycin, and vincristine). Other reported promising novel therapies include ProMACE-CytaBOM (prednisone orally, doxorubicin, cyclophosphamide, etoposide-cytarabine, bleomycin, vincristine [Oncovin], methotrexate).[25] Adverse effects of chemotherapy include high mortality rates from sepsis and treatment-related toxicities. Rituximab, a chimeric monoclonal antibody with murine variable regions targeting the CD20 antigen and human IgG1-κ constant regions, has antitumor activity against CD20-expressing B-cell lymphomas. Early experiences with rituximab (two to six weekly doses of 375 mg/m^2) in patients with PTLD (in conjunction with reduction in immunosuppression) have shown promising results. Complete remission rates of 30% to 60% have been reported.[24] Although the response rates appear to vary substantially among patients and centers, rituximab in conjunction with reduction in immunosuppression is evolving as the treatment of choice for CD20$^+$ PTLD. The role of cytokine-based therapy, such as interferon alfa and anti–IL-6, remains poorly defined[25]; increased risk of allograft rejection is seen with anti–IL-6 treatment. Sirolimus, an immunosuppressant with antiproliferative properties, has been demonstrated to prevent proliferation of B-cell (but not T-cell) PTLD-derived tumor cell lines *in vitro* and *in vivo*.[26] Limited data from nine European transplant centers have shown tumor regression in 15 of 19 patients with PTLD who underwent minimization or withdrawal of CNIs and sirolimus conversion.[27]

Factors that adversely affect survival include multiple- versus single-site involvement, increasing age, B-cell predominance, use of antilymphocyte globulin or antithymocyte globulin and OKT3, and "early" versus "late" onset (within 6 to 12 months versus more than 12 months). In recipients of renal transplants with PTLD restricted to the allograft alone, transplant nephrectomy may improve survival.

Suggested Tumor-Free Waiting Periods for Commonly Encountered Pretransplantation Malignant Neoplasms

Cancer Type	Waiting Period
Renal	
Incidental, asymptomatic	None
Large, infiltrating	At least 2 years
Wilms' tumor	At least 2 years
Bladder	
In situ	None
Invasive	At least 2 years
Uterus	
In situ cervical	None
Invasive cervical	5 years
Uterine body	At least 2 years
Breast†	At least 5 years
Colorectal‡	At least 5 years
Prostate	At least 2 years
Lymphoma	At least 2 years
Lung cancer	At least 2 years
Skin	
Melanoma§	At least 5 years
Squamous cell	Surveillance
Basal cell	None

Figure 101.12 Suggested guidelines for tumor-free waiting periods for commonly encountered pretransplantation malignant neoplasms. Consultation service is available through the Israel Penn International Transplant Registry website, *www.ipittr.org*. †Early *in situ* (e.g., ductal carcinoma *in situ*) may require only a 2-year wait. Individuals with advanced breast cancer (stage III or IV) should be advised against transplantation. ‡In patients with localized disease (Dukes' stage A or B1), a 2- to 5-year waiting period may be sufficient. §*In situ* melanoma may require a shorter waiting period of 2 years (dermatology consultation is probably warranted).

Skin Cancers

Skin cancers are the most common *de novo* post-transplantation tumors in the adult transplant population and may occur 20 to 30 years earlier in immunosuppressed patients compared with the general population. The incidence of skin cancers is 20 times higher in sun-exposed areas and 7 times higher in non–sun-exposed areas. The use of sirolimus, an inhibitor of mammalian target of rapamycin (mTOR)–induced signaling, may delay the onset or reduce the incidence of post-transplantation skin and non-skin malignant neoplasms (discussed under management of post-transplantation malignant neoplasms).[28,29]

Risk factors for skin cancer include light skin color, intensity of sun exposure (ultraviolet light exposure), genetic factors, and duration of follow-up after transplantation. In addition, immunosuppression in combination with enhanced sunlight exposure may induce malignant changes in papilloma-induced warts.

Management of Immunosuppressive Therapy in Post-Transplantation Malignant Neoplasms

There is no consensus on the management of immunosuppressive therapy in patients with post-transplantation malignant neoplasms. It has been proposed by experts in the field that immunosuppression dose reduction or withdrawal may permit recovery of the immune system and control the progression of life-threatening malignant neoplasms. The former allows intact immune surveillance against malignant cells. Nonetheless, this approach is not without its attendant risk of graft rejection and graft loss. Furthermore, little is known as to how much and to what extent immunosuppression reduction or withdrawal might alter the natural history of established post-transplantation malignant neoplasms. In our opinion, CNI to sirolimus switch or CNI minimization in conjunction with sirolimus may be a viable therapeutic option (the antitumoral effect of sirolimus is discussed later). In patients with metastatic cancer, manipulation of immunosuppression is probably futile, and the risk of rejection and graft loss necessitating a return to dialysis is likely to outweigh the benefit.

Studies suggest that immunosuppressive agents have different effects on cancer risk after transplantation. The carcinogenic effects of OKT3, antithymocyte globulin, cyclosporine, tacrolimus, and azathioprine have been well documented. In contrast to azathioprine, MMF has been shown to have antiproliferative effects and has been suggested to protect against post-transplantation malignant neoplasms.[30,31] Analysis of more than 17,000 adult patients with preexisting DM indicated a significantly higher incidence of malignant transformation in azathioprine-treated than in MMF-treated patients (3.7% versus 2.2%; $P < .01$).[31] However, whether MMF is protective of post-transplantation malignant neoplasia remains speculative.

Both preclinical and clinical studies have demonstrated that mTOR inhibitors such as sirolimus and everolimus have antiproliferative and antitumor effects. Early studies in renal transplant recipients demonstrated a lower incidence of skin cancer with sirolimus-based therapy without cyclosporine *or* sirolimus maintenance therapy after early cyclosporine withdrawal compared with those who remained on cyclosporine and sirolimus combination therapy. It has been suggested that the protective effect of sirolimus against skin cancer is due to its inhibition of several ultraviolet light–induced mechanisms involved in skin carcinogenesis. The 5-year malignancy data of the Rapamune Maintenance Regimen trial demonstrated a lower incidence of both skin and non-skin cancers at 5 years after transplantation in recipients receiving sirolimus-based therapy and cyclosporine withdrawal at month 3 compared with those receiving sirolimus and cyclosporine combination therapy.[29] Sirolimus therapy has also been reported to result in successful clinical and histologic remission of Kaposi's sarcoma in renal transplant recipients.[32] Although sirolimus appears to provide satisfactory outcomes in certain cancers after transplantation, its use in the management of malignant disease after solid organ transplantation remains to be defined and should be tailored to each individual patient.

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