

Common Infections in Kidney Transplant Recipients

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Summary

Infections are a major cause of morbidity and mortality in kidney transplant recipients. To some extent, these may be preventable. Careful pretransplant screening, immunization, and post-transplant prophylactic antimicrobials may all reduce the risk for post-transplant infection. However, because transplant recipients may not manifest typical signs and symptoms of infection, diagnoses may be confounded. Furthermore, treatment regimens may be complicated by drug interactions and the need to maintain immunosuppression to avoid allograft rejection. This article reviews common post-transplant infections, including prophylactic, diagnostic, and treatment strategies, providing guidance regarding care of kidney transplant patients with infection.

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Infections are a common cause of morbidity and mortality after transplantation, and infections rank second as the cause of death in patients with allograft function (1). The rate of first infections in the initial 3 years after kidney transplantation is 45.0 per 100 patient-years of follow-up, as estimated using Medicare claims data collected by the U.S. Renal Data System (2). With pretransplant screening of donor and recipient, vaccination, and post-transplant surveillance and prophylaxis, the impact of infections may be reduced. This article is an overview of the more common infections in kidney transplants recipients and will review strategies for prevention and treatment of these infections.

Post-transplant infections may follow a predictable pattern with regard to timing after transplant (Figure 1) (3). The traditional paradigm has noted that early infections (within the first month) are more likely to be due to nosocomially acquired pathogens, surgical issues, and some donor-derived infections. Opportunistic pathogens occur later, often during the subsequent 5 months, reflecting the greater impact of immunosuppressive therapies. Late infections may be secondary to opportunistic pathogens or conventional ones; opportunistic pathogens are more frequently seen in patients who require greater immunosuppression or who have specific environmental exposures. It is important to note that although this time line of infections is a helpful starting point, the pattern and timing of infections may be significantly altered by the choice of immunosuppressive agents that may affect the net state of immunosuppression at different time points, as well as the choice and duration of antimicrobial prophylactic agents.

Recipient and Donor Pretransplant Screening

Pretransplant screening of potential organ donors and recipients is essential to the success of solid organ transplantation. Guidelines for pretransplant screening of donor and recipient are outlined by the American Society for Transplantation clinical practice guidelines

(4) and Kidney Disease: Improving Global Outcomes (KDIGO) (5). These guidelines suggest exclusionary criteria for transplantation (based on conditions associated with poor outcomes after transplantation) and identify groups at high risk for post-transplant infections, thereby allowing for the implementation of preventive interventions. Recommended screening tests for donors and recipients are listed in Table 1. Augmented screening is recommended on a regional basis for endemic or epidemic infections, such as West Nile virus infection, Chagas disease (infection with *Trypanosoma cruzi*), and strongyloidiasis (4).

Vaccination

Vaccination is a potentially effective mechanism for preventing common infections in kidney transplants recipients, although it is notable that there are limited data regarding the efficacy, durability, and safety of these vaccines in patients with CKD, including those undergoing dialysis. Because transplant recipients tend not to respond as well to vaccines as do healthy individuals, it is important to make sure that all potential candidates for transplant have their vaccine status assessed and updated as per the standard recommendations issued annually by the Advisory Committee on Immunization Practices (6). It is especially important to make sure that transplant candidates are immunized with pneumococcal vaccine, hepatitis B virus (HBV) vaccine, and influenza vaccine (6). Patients who are not immune to varicella should also be vaccinated, with completion of the series a minimum of 2–4 weeks before transplantation. Whether age-appropriate transplant candidates who have had varicella should receive zoster vaccine is unknown because the safety and efficacy of this vaccine have not been established in patients with CKD. During the H1N1 pandemic, vaccination of transplant recipient in a case cohort study found higher incidence of greater than grade 2 cellular rejection in heart transplant recipient and *de novo* production of anti-HLA antibodies in kidney

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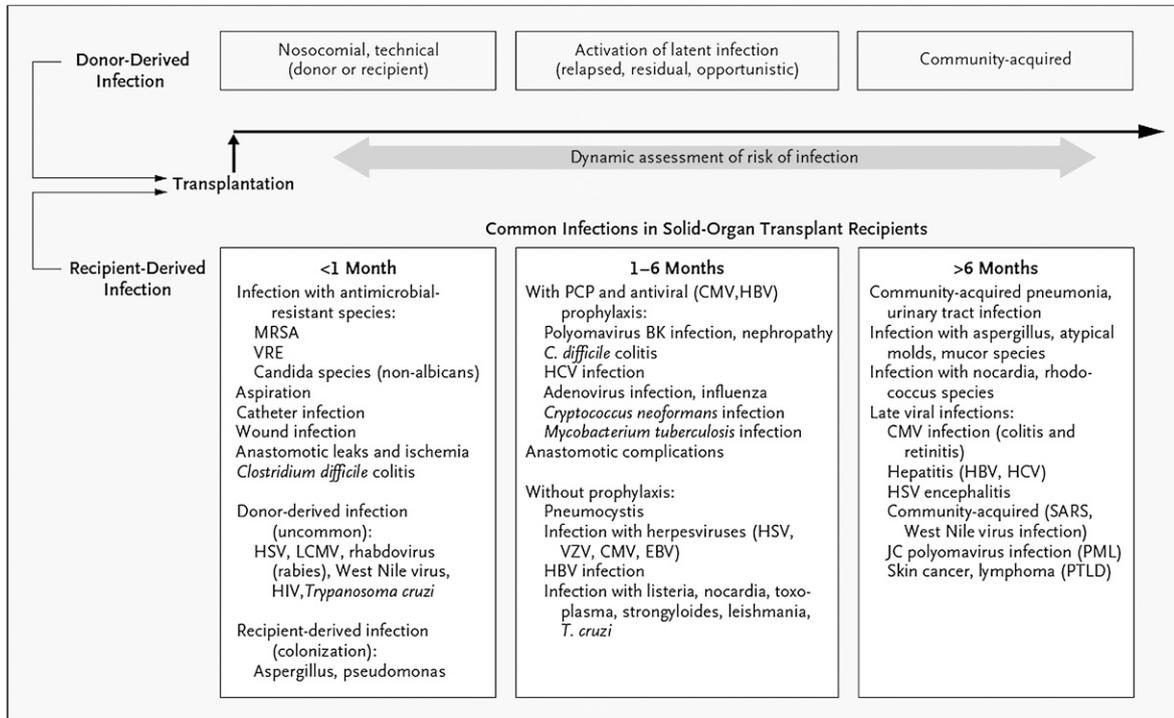


Figure 1. | Timeline of common infections in transplant recipients. CMV, cytomegalovirus; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HSV, herpes simplex virus; LCMV, lymphocytic choriomeningitis; MRSA, methicillin-resistant *Staphylococcus aureus*; PCP, *Pneumocystis jirovecii* pneumonia; PML, progressive multifocal leukoencephalopathy; PTLT, post-transplant lymphoproliferative disorder; VRE, vancomycin-resistant enterococci; VZV, varicella-zoster virus. Reprinted from reference 3, with permission.

transplants recipients. However, the clinical significance of these findings remains unknown (7,8). Per KDIGO guidelines, all kidney transplant recipients should be given inactivated vaccines and live vaccines should be avoided in all but exceptional circumstances. Because of the potential blunting of the immune response related to high-dose immunosuppression in the first 6 months after transplant, it is recommended that routine vaccination be delayed for the first 6 months. However, the effect of immunosuppression on immune memory cells is not completely understood, and the specific life span of memory T cells has not been determined in transplant patients (9). Consequently, there are no specific evidence-based guidelines for the optimal timing of vaccination after transplantation. Because of the recent influenza pandemic experience and in the absence of specific data, influenza vaccine has been considered to be an exception to the 6-month recommendation; this vaccine can be given at 1 month after transplantation in pandemic situations or as early as 3 months based on the timing of transplantation relative to the onset of the influenza season (10).

Cytomegalovirus Infection

Cytomegalovirus (CMV) infection is the most common opportunistic infection in kidney transplant recipients, occurring in 8% of patients (11). Risk factors for the development of CMV include donor seropositivity (especially if the recipient is seronegative), use of induction immunosuppression (T cell-depleting antibodies), simultaneous

kidney-pancreas transplantation, older donors (>60 years), presence of allograft rejection, and concurrent infection from other viruses (12). Antilymphocyte antibody is associated with a two- to five-fold increase in rate of CMV, but basiliximab and daclizumab do not seem to increase its incidence (12,13). The incidence of CMV disease in donor CMV-seronegative/recipient CMV-seronegative (CMV D- /R-) is <5% (5).

Distinguishing CMV infection from CMV disease may be important in considering treatment options. CMV infection is defined as evidence of CMV replication regardless of symptoms, and CMV disease requires both evidence of infection as well as symptoms, including viral syndrome with fever or malaise, leukopenia, thrombocytopenia, or evidence of tissue invasion (e.g., pneumonitis, hepatitis, retinitis, gastrointestinal disease) (14). CMV infection may occur as primary infection, reinfection (both donor-derived), or reactivation of latent recipient infection (15). Donor-derived infections are the most common.

In addition to the direct effects of infection, CMV also has been associated with important indirect effects, including diminished patient and graft survival. These include increased immunosuppression, as reflected by the development of other opportunistic infections. Additionally, CMV infection within 100 days of transplant is an independent risk factor for overall recipient mortality, and early CMV disease is associated with increased cardiovascular mortality beyond 100 days (12). Reischig and colleagues found that CMV disease is an independent risk factor for biopsy-proven acute rejection in the first 12 months (16). CMV

Table 1. Donor and recipient screening are based on epidemiologic history and serologic findings

Test	Donor	Recipient	Action
CMV IgG antibody	√	√	Prophylaxis per guidelines
EBV antibody IgG	√	√	Monitoring related to donor and recipient serostatus (D+/R-)
HSV IgG antibody	√	√	Herpes-specific prophylaxis for CMV D- /R-
HIV antibody	√	√	Exclude donor; recipients considered if stable/controlled HIV
HTLV-1/2 antibody	√	√	Exclude donor with HTLV-1
VZV antibody	NA	√	Consider vaccination before transplant for nonimmune patients; zoster vaccine might be considered before transplant for candidates age ≥60 yr
HCV antibody with nucleic acid test for all candidates and high-risk donors	√	√	HCV-positive donors reserved for HCV-positive recipients; HCV-positive recipients should undergo liver biopsy before listing
HBV: HBsAg	√	√	Exclude donor
HBV: anti-HBsAg	√	√	All candidates should be vaccinated if they do not have evidence of antibody to HBV
HBV: HBcAb IgM/IgG	√	√	Donors with isolated positivity for antibody to HBcAb should be tested with IgM; if positive on IgM testing, patient should be excluded from donation. Isolated HBcAb IgG-positive donors can be considered, preferably for recipients with evidence of immunity to HBV.
RPR, VDRL	√	√	Recipient will need penicillin if donor or recipient tested positive and confirmed with treponemal-specific test and not treated
Tetanus diphtheria and acellular pertussis	NA	√	Facilitate vaccination before transplant for patients who have not been vaccinated in adulthood
Measles, mumps, and rubella	NA	√	Facilitate vaccination for nonimmune candidates (not to be given after transplant)
Pneumococcal vaccine	NA	√	Facilitate vaccination pre transplant
Influenza vaccine	NA	√	Seasonal
PPD or interferon-γ release assay for latent TB	√ (live donors)	√	Evaluate for active TB (live donors and recipients) and delay transplant until treatment for active TB. Donors and recipients with latent infection should receive standard treatment (if not previously completed). If donor declines treatment, can consider use of organ with treatment of recipient. Recipient treatment can be completed before or after transplant; if possible, it is preferable to complete treatment before transplant.
Other screening			
Infection history (including environmental/geographic exposures; prior infections, including UTIs; vaccination)			
Chest radiography			
Optional: <i>Strongyloides</i> , <i>Coccidioides</i> , <i>Histoplasma</i> , West Nile serologic testing based on exposure			
CMV, cytomegalovirus; EBV Epstein-Barr virus; D, donor; R, recipient; HSV, herpes simplex virus; HTLV, human T cell lymphotropic virus; VZV, varicella-zoster virus; HCV, hepatitis C virus; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; anti-HBsAg antibodies against hepatitis B surface antigen; HBcAb, hepatitis B core antibody; RPR, rapid plasma regain; VDRL, Venereal Disease Research Laboratory; NA, not applicable; PPD, purified protein derivative; TB, tuberculosis; UTI, urinary tract infection. X, do not perform; √, perform			

disease is also associated with post-transplant lymphoproliferative disorder (PTLD), transplant renal artery stenosis, post-transplant diabetes mellitus irrespective of immunosuppressive drugs, and recurrent thrombotic microangiopathy after kidney transplant (17–19). In renal transplant recipients, Richardson *et al.* in 1981 posited that systemic CMV infection was linked to glomerulopathy characterized by enlargement or necrosis of endothelial cells and

accumulation of mononuclear cells and fibrillar material in glomerular capillaries; however, this finding has subsequently been questioned (20,21).

Because of the significant effect of CMV on transplant outcomes, preventing this infection has received a lot of attention. Administration of antiviral agent to at-risk post-transplant patients before the onset of infection (prophylaxis) or when infection has been identified (pre-emptive

therapy) has been studied and found to be effective at reducing the incidence of CMV disease (22–24). In the highest-risk population (D+/R–), chemoprophylaxis has reduced the incidence of CMV disease by 60% and has decreased the incidence of CMV-associated mortality and opportunistic infection (22). Pre-emptive therapy in high-risk patients based on CMV viral load monitoring has not shown any reduction in CMV-related mortality (24). A randomized, controlled trial published in 2008 comparing oral ganciclovir chemoprophylaxis with viral load monitoring in kidney transplant recipients revealed improved graft survival in those who received ganciclovir chemoprophylaxis (25). For this reason, prophylaxis is generally recommended for the highest-risk recipients (5). However, the use of CMV viral load monitoring and pre-emptive antiviral treatment with ganciclovir in lower- (D–) and moderate-risk (CMV D+/R+) recipients has been shown to be effective and could be considered in these patients (24). A comparison of universal prophylaxis with pre-emptive therapy is shown in Table 2 (26).

Standard prophylactic guidelines recommend therapy in D+/R–, D+/R+, and D–/R+ using valganciclovir or oral ganciclovir (if available) for a minimum of 3 months after transplantation and 1–3 months after treatment with antilymphocyte antibody (14,26). For the highest-risk recipients (CMV D+/R–), intravenous ganciclovir might also be considered. Although early studies showed benefit with oral or intravenous acyclovir, this has been shown to be inferior to ganciclovir (23). More recently, valganciclovir has replaced ganciclovir because of the lower pill burden, better bioavailability, and reduced availability of oral ganciclovir (27). The optimal duration of prophylaxis

is not known, but recent trials suggested that 6 months' prophylaxis is more effective in decreasing incidence of CMV disease and late-onset CMV disease in D+/R– kidney transplant recipients (28,29). Because blood products may be a source of CMV infection in CMV D–/R– recipients, whenever possible, these patients should receive CMV-negative blood and leukodepleted blood during or after transplantation.

CMV disease should be considered in all at-risk transplant recipients presenting with consistent signs and symptoms (including fever, cytopenias, and gastrointestinal symptoms), especially during the first year after completion of prophylaxis. Current diagnostic strategies rely on the detection of CMV viremia; antibody testing and culture are less sensitive and delay diagnosis. Viremia may be detected using the CMV antigenemia assay or by nucleic acid testing (NAT); the latter is generally more sensitive (14,26). Typically, higher values are more reflective of CMV disease and viral load can be followed (usually weekly) to chart the response to therapy. Historically, NAT had statistically significant interlaboratory variability, and it was recommended that all individual patient testing be conducted in the same laboratory (5,26,30,31). International standards for CMV testing have recently been established, and this should ultimately reduce this variability. Of note, not all patients with CMV disease exhibit viremia, and histopathologic confirmation may be required for diagnosis, especially for patients with gastrointestinal disease.

Treatment of established CMV disease requires a multifactorial approach, including reduction of immunosuppressive agents, antiviral agents, and in some cases adjuvant therapy (14,26). Intravenous ganciclovir has been considered the mainstay of therapy. However, the Valcyte in CMV-Disease Treatment of Solid Organ Recipients (VICTOR) trial found that valganciclovir was as effective as intravenous ganciclovir in at least some solid organ transplant recipients with mild to moderate disease (32). Current guidelines recommend valganciclovir, 900 mg twice daily, or intravenous ganciclovir, 5 mg/kg twice daily (adjusted for renal insufficiency), for mild CMV disease (26). For patients with life-threatening CMV disease, high viral loads, leukopenia, and impaired absorption, intravenous ganciclovir is preferable and maintenance immunosuppression should be decreased despite the potential risk of rejection (12). Administration of CMV-specific hyperimmune globulin or standard intravenous immunoglobulin may be considered as adjuvant therapy in individuals with hypogammaglobulinemia, failure to respond to standard therapy, or severe systemic infection (28).

If CMV disease worsens or the viral load increases despite 2 weeks of therapy, ganciclovir resistance should be considered (33). CMV resistance is usually attributed to prolonged exposure to subtherapeutic ganciclovir (especially with oral ganciclovir); however, recently Couzi *et al.* found a higher incidence of drug resistance CMV (UL97 or UL54 mutation) in pre-emptively treated D+R– kidney transplant recipients, demonstrating that resistance can be seen even in shorter exposures to ganciclovir and its analogues (34). Resistance can be identified by genotype testing for mutations of the genes encoding UL97 and UL54. Management of resistant infections includes reduction of immunosuppression and adjustment of antiviral

Table 2. Comparison of known benefits and limitations of prophylaxis versus pre-emptive therapy

Effect	Prophylaxis	Pre-Emptive
CMV disease	+++	+++
Late CMV disease	++	–
CMV relapse	++	++
CMV treatment failure	+++	+
Fewer opportunistic infections	++	–
Improved graft survival	++	–
Prevention of rejection	+	–
Survival	+	–
Other viruses	+	–
Post-transplant lymphoma	++	+++
Kaposi sarcoma	+++	+
Safety	+	+++
Easier logistics	+++	+
Lower drug cost	+	+++
Lower monitoring cost	+++	+
Resistant CMV	++	+

+, ease of use and strength of evidence; ++, intermediate evidence; +++, strongest evidence or favors the approach listed; –, no evidence exists. CMV, cytomegalovirus. Reprinted from reference 26, with permission.

treatment to alternate antiviral agents to which the virus is susceptible. No controlled comparative trial data are available regarding optimal alternate therapy for drug-resistant CMV; high-dose ganciclovir (for specific genetic mutations), foscarnet, and cidofovir have been used effectively. A treatment algorithm for patients suspected of having resistant infection was proposed by an international CMV consensus conference and is shown in Figure 2 (26).

EBV Infection and PTLD

Although less common than CMV, Epstein-Barr virus (EBV) is a significant cause of post-transplant morbidity and mortality because of its association with the development of PTLD. This condition is defined as lymphoid proliferation arising in transplant recipients and may present in many different organs, including the allograft. This can be polymorphic or monomorphic, and usually involves B cells. Approximately 62%–79% of PTLD cases have been associated with EBV. EBV-naïve recipients who receive EBV-seropositive organs are at greatest risk for PTLD; consequently, PTLD is most frequently seen in younger populations (5). EBV-associated PTLD usually occurs in the first year after transplant. The risk factors for early PTLD include primary EBV infection, younger recipient, CMV disease, OKT3 or polyclonal antilymphocyte antibody administration, and the type of organ transplanted; kidney transplant recipients are at a lower risk compared with recipients of other types of transplants (35). EBV disease may present with a nonspecific febrile syndrome, lymphadenopathy, hepatosplenomegaly, and atypical lymphocytosis. Other manifestations include organ-specific disease (gastroenteritis, hepatitis, or pneumonitis) and hematologic disorders, including leukopenia, thrombocytopenia, hemolytic anemia, and hemophagocytosis (35). Primary EBV infection in EBV-seronegative recipients usually occurs in the first 3–6 months (5). PTLD typically follows primary infection. Diagnosis of PTLD requires histologic confirmation, preferably *via* excision biopsy with immunologic cell-typing, cytogenetics, immunoglobulin gene arrangements, and EBV-specific staining (35). Staging is based on location, metastasis, and histologic type (monoclonal, polyclonal, T cell, or B cell). Observational studies have shown 50% mortality from EBV-associated PTLD (36,37).

Currently there is no consensus regarding the treatment of PTLD, but reduction of immunosuppression is routinely used and can lead to remission in 23%–86% of patients (33). Although antiviral therapy has been used alone or with immunoglobulin, no evidence supports its efficacy (35). Additional therapeutic interventions have included surgery, monoclonal antibody therapy, chemotherapy, and radiation. Rituximab (monoclonal antibody to CD20) is commonly used to treat EBV-positive PTLD in patients requiring therapy beyond immunosuppression reduction (35). In some cases with persistent disease, PTLD isolated to the allograft may warrant surgical resection of the allograft (33). Chemotherapy should be administered in patients in whom rituximab fails, those with EBV-negative PTLD, and those requiring a rapid response (38). In patients who achieve complete remission but lose their allograft, retransplantation has been successful (33). Patients with isolated allograft involvement have a 5-year survival rate

of 68% compared with 36%–38% in kidney transplant recipients with PTLD extending beyond the allograft (33).

There is no standardized therapy to prevent PTLD; however, effective prevention of CMV may prevent EBV disease by limiting immunomodulation by CMV infection (39). KDIGO guidelines propose monitoring EBV viral load by NAT in the first post-transplant week, then monthly for the first 3–6 months, then every 3 months until the end of first post-transplant year; viral load should also be monitored after acute rejection therapy in high-risk groups (*i.e.*, pediatric patients and EBV D+/R– kidney transplant recipients). Viral load monitoring identifies recipients with rapidly increasing viral loads who are risk of developing PTLD and allows for the timely reduction of immunosuppression before the development of PTLD (5). Patients with primary EBV, CMV, and hepatitis C virus (HCV) infection are at higher risk for PTLD and should be followed closely.

BK Polyoma Virus Infection

BK polyoma virus (BKV) is a member of the polyoma family of viruses that has been associated with polyomavirus-associated nephropathy (PyVAN) and polyomavirus-associated hemorrhagic cystitis (40). PyVAN affects up to 10% of kidney transplant recipients, and the rate of renal allograft loss varies from 10% to 80% (41,42). About 30%–50% of kidney transplant recipients with high-level viremia progress to BKV viremia and PyVAN (40). BKV viremia usually precedes BKV nephropathy by a median of 8 weeks. Approximately, 50% of patients who develop BKV viremia will do so by 3 months after transplantation. Most BKV nephropathy occurs in the first 2 years after transplant, with only 5% of cases occurring between 2 and 5 years after transplantation (43).

Most kidney transplant recipients with PyVAN manifest with renal dysfunction; less commonly, patients will develop ureteric obstruction from stenosis or stricture (44). Risk factors for PyVAN include high levels of immunosuppression, recipient characteristics (including older age, male sex, and decreased BK virus-specific T cell activation), and donor characteristics (including female sex, deceased donation, increased cold ischemia time, HLA mismatch, and African-American ethnicity) (40).

Diagnosis of BK virus infection relies on the detection of the virus in blood (whole blood, plasma, or serum), urine, or renal tissue by detection of viral cytopathic effect (decoy cells), NAT, BKV-specific antibody, or pathology (44). The use of NAT to detect BKV in plasma provides a sensitive method for identifying BKV infection and determining kidney transplant recipients who are at increased risk for BKV nephropathy. Consequently, KDIGO guidelines recommend routine screening of plasma after transplantation. BKV plasma NAT results of $>4 \log_{10}$ genome equivalents/ml have a high positive predictive value, and a negative urine NAT result has an almost 100% negative predictive value (5,44). Kidney transplant recipients with sustained plasma BKV levels $>4 \log_{10}$ genome equivalents/ml for >3 weeks should undergo allograft biopsy to evaluate for PyVAN (5,40). Buehrig *et al.* found superior prognosis for PyVAN in renal transplant recipients in whom the diagnosis was based on a surveillance allograft biopsy (45).

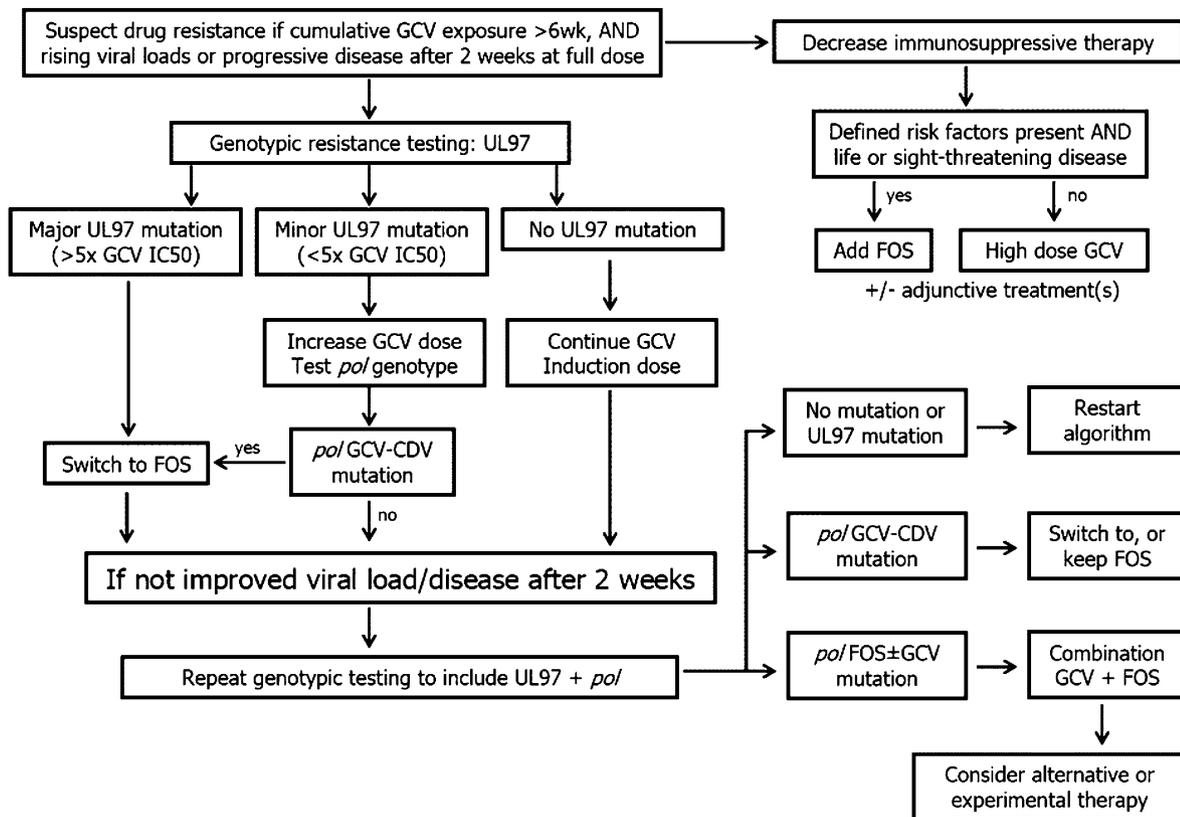


Figure 2. | Suggested algorithm for management of suspected cytomegalovirus (CMV) drug resistance. CDV, cidofovir; FOS, foscarnet; GCV, ganciclovir; IC50, 50% inhibitory concentration. Reprinted from reference 26, with permission.

This earlier identification, before the onset of a significant increase in serum creatinine, demonstrated a lesser degree of interstitial fibrosis at diagnosis with lower baseline serum creatinine. Histopathologic diagnosis of PyVAN requires a minimum of two cores on biopsy; the presence of intranuclear polyomavirus inclusion bodies in tubular epithelial or glomerular parietal cells with epithelial cell necrosis and acute tubular injury and immunohistochemical detection of SV40 T antigen are diagnostic of PyVAN (40,44).

All kidney transplant recipients should be screened for BKV with quantitative plasma NAT at least monthly for the first 3–6 months after transplant, every 3 months until the end of the second year if an unexplained increase in serum creatinine occurs; and after treatment for acute rejection (5,40). A positive result on a screening test by quantification of DNA load in the urine (threshold >7 log₁₀ genome equivalents), urine viral capsid protein mRNA (threshold >6.5×10⁵ copies/ng total RNA), or plasma DNA load (threshold >4 log₁₀ genome equivalents) or biopsy-proven PyVAN should prompt consideration for reduction of immunosuppression (44). Treatment options for BKV replication and disease from KDIGO guidelines are shown in Table 3. Tacrolimus trough levels are targeted to <6 ng/ml and cyclosporine levels to <150 ng/ml in the presence of persistent viremia (>3 weeks of >4 log genome equivalents/ml) (5). Patients with sustained high plasma BKV levels despite reduced immunosuppressive dosing may need antiviral therapy. No definitive evidence

supports the use of adjuvant antimicrobial therapy, although anecdotal reports have supported the use of cidofovir or leflunomide for treatment (46–48). Although it is suspected that the choice of immunosuppression may affect response to therapy, there is no specific recommendation to direct the choice of immunosuppression in patients with BKV infection. Of note, patients who experience allograft loss due to PyVAN have undergone successful retransplantation (44).

HCV Infection

HCV is an important cause of morbidity and mortality in kidney transplant recipients. HCV has been increasingly recognized in patients with ESRD. Infection with HCV may also occur after transplantation; donor-derived infection is an important although uncommon source of infection. It is important to recognize the presence of HCV before transplantation; screening of patients with ESRD should include NAT because antibody formation may be impaired in this population (49). Antibody production after transplant is also impaired; consequently, testing kidney transplant recipients for newly acquired HCV should also include NAT (50). One study of donor-derived HCV demonstrated anti-HCV antibody response in only 6 of 14 recipients, with first detection of antibody delayed for >300 days (51). Moreover, HCV infection may not be associated with abnormal liver function test results. Thus, it is essential that HCV RNA be obtained for all at-risk recipients,

Table 3. Treatment of BK nephropathy by modification of maintenance immunosuppression

Switching	Decreasing	Discontinuing
Tacrolimus → CsA (trough level 100–150 ng/ml) (B-III) MMF → azathioprine (dosing ≤ 100 mg/d) (B-III)	Tacrolimus (trough levels < 6 ng/ml) (B-III) MMF dosing ≤ 1 g/d (B-III)	Tacrolimus or MMF (maintain or switch to dual drug therapy) CsA/prednisolone (B-III)
Tacrolimus → sirolimus (trough levels < 6 ng/ml) (C-III) MMF → sirolimus (trough levels < 6 ng/ml) (C-III) MMF → leflunomide (C-III)	CsA (trough levels 100–150 ng/ml) (B-III)	Tacrolimus/prednisolone (B-III) Sirolimus/prednisone (C-III) MMF/prednisone (C-III)

CsA, cyclosporine A; MMF, mycophenolate mofetil B-III, moderate evidence to support a recommendation for use based on evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees; C-III, poor evidence to support a recommendation based on evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees. Reprinted from reference 5, with permission.

based either on the recipient or the donor's risk profile, as well as for those with abnormal liver enzyme levels.

Kidney transplant recipients infected with HCV have decreased survival and increased complication rates regardless of the timing of acquisition (52). It is important to identify advanced liver disease in candidates for kidney transplantation before transplantation to limit the risk for a poor outcome; consequently, all HCV-positive candidates should undergo liver biopsy. Post-transplant complications include GN, post-transplant diabetes mellitus, and accelerated progression to cirrhosis with fibrosing cholestatic hepatitis (50,52–55). Viral loads typically increase to high levels after transplantation, regardless of the degree of liver disease, and about 20%–51% of patients may have normal liver enzyme levels with abnormal histologic features; this makes noninvasive monitoring of kidney transplant recipients with HCV infection more difficult. Thus, protocol liver biopsies within 6–12 months of transplantation, with subsequent biopsies based on clinical course, are required for evaluation of liver disease after transplantation (53). The prevalence of cirrhosis has been reported to be 5%–21% after 3–7 years of follow-up (56,57). In one study of sequential liver biopsies in 51 kidney transplant recipients every 3–4 years, 40% of the patients had progression of fibrosis, 40% had stable levels of fibrosis, and 20% showed regression of fibrosis >10 years after transplantation (58). Glomerular diseases described in kidney transplant recipients include cryoglobulinemic or noncryoglobulinemic membranoproliferative GN and membranous GN (53). HCV-infected recipients should be tested for proteinuria every 3–6 months, and patients with new-onset proteinuria (urine protein-to-creatinine ratio >1 or 24-hour urine protein >1 g) should undergo allograft biopsy (5).

Because of the potential for improved outcomes with successful treatment of HCV before transplantation and the added complications of treating transplant recipients, it is preferable to treat candidates with HCV before transplantation on the basis of liver biopsy findings. Response to interferon (IFN) has varied, with rates between 20% and 90%, in part depending on HCV genotype (59). Ribavirin is generally contraindicated in renal failure because of the risk for hemolytic anemia, and there is insufficient data on

newer protease inhibitor treatments in patients with renal failure. Patients with a sustained virologic response to pre-transplant treatment with interferon have a reduced risk for HCV recurrence and decreased post-transplant GN (60). IFN α is associated with an increased risk for allograft dysfunction and rejection, making post-transplant treatment more difficult. Consequently, HCV-infected kidney transplant recipients should be treated (in conjunction with hepatology or infectious disease experts) only if the benefits outweigh the risk for rejection (61). The effect of immunosuppression on the progression of HCV-related liver injury and survival remains uncertain, although in general more intensive immunosuppression (including the use of OKT3 and antithymocyte globulin) has been associated with increased liver disease. A study among liver transplant recipients with recurrent HCV infection found sirolimus was associated with reduced fibrosis and rate of progression (62). However, the use of sirolimus has not been shown to be advantageous in kidney transplant recipients with recurrent HCV infection. The optimal management of immunosuppression in HCV-infected kidney transplant recipients has not been defined.

HBV Infection

Patients undergoing dialysis are at increased risk for contracting HBV, although the prevalence of hepatitis B surface antigen (HBsAg)-positive patients has declined because of HBV vaccination, strict segregation of HBsAg-positive patients in dialysis units, improved screening of blood products, and the use of erythropoiesis-stimulating agents. About 2%–10% of patients with a history of HCV infection before transplantation will have reactivated HCV infection after transplantation (33). Because of the availability of antiviral agents, patients with chronic hepatitis B and cleared viremia can now be considered for transplantation.

Recognition of HBV liver disease after transplantation may be difficult because clinical clues, especially liver enzyme levels, may not accurately reflect infection status. Serial monitoring of HBV DNA every 3–6 months is required, and elevated viral loads suggest resistance to therapy (50). In the absence of specific antiviral therapy, a study found that histologic deterioration occurred in 85.3% of 101

patients at a mean interval of 66 months (63). Meta-analysis by Fabrizi *et al.* indicates HBsAg as an independent risk factor for post-transplant death and allograft loss (64). Notably, these studies did not fully evaluate the effect of all currently available antiviral agents on outcomes.

At least 24 months of prophylactic treatment (5) is recommended at the time of transplantation, irrespective of HBV DNA, to suppress viral replication and prevent hepatic fibrosis (65). However, the optimal treatment duration is unknown because of a high potential for relapse associated with withdrawal of antiviral agents. Seven options are currently approved for the treatment of chronic hepatitis B: IFN α , pegylated IFN, lamivudine, entecavir, telbivudine, tenofovir, and adefovir (64,66,67). IFN should be avoided because of the high incidence of rejection. Entecavir is associated with the lowest rate of drug resistance, with rates <1% in 5 years among treatment-naive patients (67). Because of the potential for emergence of resistance in kidney transplant recipients treated with lamivudine, KDIGO recommends tenofovir or entecavir as preferable to lamivudine unless cost is an issue (5). On the basis of available data, it is recommended that treatment be initiated at the time of transplantation, irrespective of HBV DNA, to suppress viral replication and prevent hepatic fibrosis (5). Viral replication has been related to the net state of immunosuppression and not to any individual immunosuppressive agent. Consequently, KDIGO recommends maintaining the lowest possible steroid dose and minimizing doses of all immunosuppressive medications in patients with HBV infection (5). HBsAg-positive kidney transplant recipients should be screened for hepatocellular carcinoma with α -fetoprotein and liver ultrasonography every 12 months (5).

HIV Infection

Although HIV traditionally was considered a contraindication to transplantation, recent data suggest that selected patients can undergo successful transplantation with survival rates similar to those of kidney transplant recipients age ≥ 65 years (68). Candidates for transplantation include those with well controlled HIV infection, as manifested by CD4 counts >200 cells/ μ l, undetectable HIV viral loads, and the absence of untreatable infections or malignancies (69). Thus far, the most significant complications after transplantation in this population are markedly increased rejection rates, difficulties managing the pharmacokinetic interactions between antiretroviral agents and immunosuppressive medications, and complications related to cardiovascular risk factors and hepatitis coinfection (69). Of note, opportunistic infections and progression of HIV infection have not occurred in most HIV-infected kidney transplant recipients.

Optimal care of kidney transplant recipients with HIV requires meticulous attention to antiretroviral and immunosuppressive drug interactions and close monitoring for rejection. Whenever possible, it is preferable to avoid the use of protease inhibitors, which have the most significant interactions with these immunosuppressive agents. However, the choice of antiretroviral agents should reflect HIV susceptibility test results and be coordinated with the patient's HIV provider.

The choice of immunosuppressive medication may have a substantial effect on HIV management (69,70). Notably, anti-thymocyte globulin results in profound and lasting CD4 suppression and should be restricted to patients with high immunologic risk for rejection (70,71). Monoclonal anti-IL2 receptor antibodies, such as basiliximab/daclizumab, have been shown to increase CD4 counts and are used in some centers as induction therapy (70). Tacrolimus appears to be preferable to cyclosporine with respect to rejection risk, and mycophenolate has inhibitory effects on HIV replication *in vitro* (72). In kidney transplant recipients with HIV, lifelong *Pneumocystis jiroveci* prophylaxis with trimethoprim-sulfamethoxazole is recommended (69). Because patients with HIV may be co-infected with HCV and HBV, careful evaluation for these infections should precede transplantation; liver biopsies should be performed before transplantation in HBV- or HCV-infected candidates to exclude patients with advanced liver disease.

Urinary Tract Infection

Urinary tract infections (UTIs) are the most common bacterial infections requiring hospitalization in kidney transplant recipients, followed by pneumonia, postoperative infections, and septicemia. Women are at greatest risk for UTIs; other risk factors include deceased-donor transplant, kidney-pancreas transplantation with bladder drainage, prolonged catheterization, uretero-vesical stents, and increased immunosuppressed state (73). A retrospective cohort study of 28,942 primary renal transplant recipients from the U.S. Renal Data System database revealed a cumulative UTI incidence of 17% during the first 6 months after transplantation; at 3 years the incidence was 60% for women and 47% for men. Given the nature of data collection, these data probably underestimate the actual incidence (74).

Patients may present with classic UTI symptoms, gastrointestinal symptoms, or asymptomatic bacteriuria. *Escherichia coli* is the most common uropathogen in kidney transplant recipients. No consensus is available for management of asymptomatic bacteriuria, and a prospective randomized trial suggests that treatment of this condition beyond a year does not prevent symptomatic UTI (75). All UTIs in kidney transplant recipients are considered complicated, and thus standard treatment typically involves 7–14 days of antibiotic therapy; however, the optimal duration has never been studied. Complications of pyelonephritis, including abscesses and emphysematous pyelonephritis, require source control; this may include drainage, removal of stents and/or urinary catheters, and more prolonged antimicrobial treatment (at least 2 weeks) (76).

On the basis of very limited data, standard post-transplant management includes prophylactic treatment with trimethoprim-sulfamethoxazole for 6 months after transplantation (5). This intervention is predicated on the finding in at least one study that early UTI may be associated with diminished allograft function, at least transiently, and that trimethoprim-sulfamethoxazole prophylaxis reduces the risk for UTI threefold, without resulting in significant colonization by trimethoprim-sulfamethoxazole-resistant

gram-negative bacilli (77,78). Whether patients who are unable to receive trimethoprim-sulfamethoxazole should be given alternative prophylaxis is not known, but that option could be considered (5).

Management of kidney transplant recipients with candiduria is controversial. In one observational case-control study of 192 kidney transplant recipients with candiduria, 50% were not treated with antifungal therapy and antifungal treatment was not associated with improved clinical outcomes (79). Determination of the clinical relevance of candiduria can be difficult. The Infectious Diseases Society of America guidelines recommend treatment of asymptomatic patients with candiduria with fluconazole, 200 mg daily for 7–14 days, or intravenous amphotericin B, 0.3–1 mg/kg per day for 7 days, if the patient is undergoing a urologic procedure or is neutropenic (80,81). Symptomatic patients should be treated for a minimum of 2 weeks, and radiographic imaging should be considered to exclude the presence of abscesses, fungus balls, and other urologic abnormalities that may necessitate longer treatment or surgical intervention (81).

Treatment of fungal UTIs may be complicated because of drug interactions between antifungal agents and immunosuppressive medications, as well as differential penetration of antifungal agents into the urinary tract. Fluconazole is the drug of choice for susceptible *Candida* species; other azoles and echinocandins are not concentrated in the urinary tract and thus are less likely to be effective if infection is confined to the urinary tract (80,81). In fluconazole-resistant cases, liposomal amphotericin and 5-flucytosine might be considered (80). Because of the substantial drug interaction between azoles and calcineurin inhibitors and mammalian target of rapamycin (mTOR) inhibitors, institution of azole therapy should be accompanied by dose reduction of calcineurin inhibitors and mTOR inhibitors at the initiation of the azole therapy (82). It is advisable to avoid coadministration of voriconazole and sirolimus because of excessive elevation of sirolimus levels.

***Mycobacterium tuberculosis* Infection**

The incidence of infection with *Mycobacterium tuberculosis* among kidney transplant recipients in North America, Europe, and India/Pakistan is 0.5%–1.0%, 0.7%–5%, and 5%–15%, respectively (83). In a French study looking at 16,184 kidney transplant recipients, tuberculosis (TB) occurred in 0.45% of kidney transplant recipients, usually in the first year (84). The effect on recipient outcome was significant, with a hospital mortality rate of 6.1% and 1-year graft survival rate of 97% (84). Only 20%–25% of all cases of active tuberculous disease occurring after transplantation occur in patients who had positive tuberculin skin test reactions before transplantation, probably reflecting the relative energy associated with renal failure rather than *de novo* infection in the post-transplant period (85). The time between transplantation and the onset of TB was significantly longer for renal transplant recipients than for other organ transplant recipients (83).

Clinical presentation of TB in immunocompromised patients differs from that in the normal host, with approximately one third of all cases of active infection involving disseminated disease or extra-pulmonary sites, compared

with approximately 15% of cases in normal hosts (83). The diagnosis of active TB in transplant recipients requires a high index of suspicion and, in some cases, biopsy for microbiologic diagnosis. Neither tuberculin skin tests nor IFN- γ release assays are appropriate for the diagnosis of active infection. Screening and identification of individuals with prior latent infection with TB are vital to reduce post-transplant infections; immunosuppression increases the risk for reactivation because of impairment of microbial-specific cytotoxic T cell response, a key host defense against mycobacterial infection. Consequently, all transplant candidates and live donors should be evaluated before transplantation to minimize the likelihood of post-transplant disease (85). Screening should include a careful history regarding previous exposures, review of previous and current results of tuberculin skin testing or IFN- γ release assay, and chest radiography. IFN- γ release assays can be used to distinguish latent TB infection from reactivity due to bacille Calmette-Guérin vaccination. Historical or radiographic evidence may be sufficient to support the diagnosis of latent infection, especially because transplant candidates may have diminished responses with either tuberculin skin test or IFN- γ release assay. Previously untreated patients with evidence of latent infection should be treated for latent TB, usually with isoniazid for 9 months (85). Organ transplantation may be performed in patients receiving treatment for latent TB.

Treatment of active disease should follow established American Thoracic Society guidelines. A four-drug regimen of isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months followed by rifampin and isoniazid alone for 4 additional months is recommended for active TB, although bone, joint, and central nervous system infection may require longer treatment (85). Because rifampin activates the CYP3A4 pathway, it can markedly reduce the levels of calcineurin inhibitors and mTOR inhibitors, increasing the potential risk for rejection. Consequently, alternative regimens excluding rifampin and in some cases including fluoroquinolones may be considered (85, 86, 87). It is important to perform susceptibility testing on all mycobacterial isolates to ensure adequacy of the treatment regimen.

***P. jiroveci* Infection**

Historically, *P. jiroveci* (formerly known as *P. carinii*) was an important cause of severe pulmonary infections during the first 3–6 months after transplantation. Currently, because of universal prophylaxis during the first 6–12 months after transplantation, this infection is now rare and the overall incidence rate of *P. jiroveci* pneumonia (PCP) in kidney transplant recipients is 0.8 case per 1000 person after completion of 1 year of prophylaxis (88). PCP is associated with a 29%–50% mortality rate in kidney transplant recipients (89).

The typical presentation of PCP includes fever, cough, shortness of breath, and hypoxia out of proportion to physical and radiologic findings. Diagnosis relies on identification of the organism in induced sputum, bronchoalveolar lavage, or transbronchial biopsy samples (89). Optimal treatment includes high-dose trimethoprim-sulfamethoxazole (15–20 mg/kg per day) in divided doses or intravenous

pentamidine (4 mg/kg per day) for 14–21 days. Potential alternative agents include atovaquone for mild to moderate PCP or the combination of clindamycin and pyrimethamine. In patients with hypoxia (partial pressure of oxygen in the alveoli < 70 mmHg on room air), corticosteroids should be coadministered with antimicrobial agents (89). Although the optimal dose of corticosteroids has not been defined in transplant recipients, the current recommendations suggest 40–60 mg prednisolone given twice daily for 5–7 days and with dose tapering over the subsequent 7–14 days (89).

Because of the potential for adverse outcomes due to PCP, prophylaxis for a minimum of 6–12 months after transplantation is recommended; longer courses may be indicated in patients requiring prolonged higher doses of immunosuppression (90). Trimethoprim-sulfamethoxazole is the preferred prophylactic agent; for patients who are intolerant or allergic, alternatives include dapsone, atovaquone, or inhaled pentamidine (although there is a higher rate of breakthrough PCP with pentamidine and administering this aerosolized medication may be costly and inconvenient) (89,91). Glucose-6 phosphate dehydrogenase levels should be measured before initiating dapsone to decrease the risk for dapsone-induced hemolysis (89).

Other Fungal Infections

Renal transplantation is associated with the lowest incidence of invasive fungal infection of all solid organ transplantations (92). Rubin *et al.* divided fungal infections in renal transplant recipients into two categories: disseminated primary or reactivation infection of “geographically restricted” mycoses (*i.e.*, those associated with specific geographic/environmental exposures, including histoplasmosis, coccidioidomycosis, blastomycosis, and paracoccidioidomycosis) versus classic opportunistic infections (*Aspergillus*, *Candida*, and *Cryptococcus* infections and zygomycoses) (75). Which infections develop depend in part on the patient’s specific exposure history as well as the nature of the exposure and the net state of immunosuppression. The three leading sites of fungal infections in hospitalized kidney transplant recipients are esophageal candidiasis, pneumonia, and urogenital candidiasis (93). Risk factors for fungal infections in transplant recipients include the use of large doses of corticosteroids, multiple or recent rejection episodes, hyperglycemia, poor transplant function, leukopenia, and older age (15).

Diagnoses of fungal infections are confounded by the diverse presentations and limitations of diagnostic testing. With the exception of *Candida* species, organisms causing fusariosis, *Cryptococcus* species, and *Histoplasma* species, it is difficult to isolate these organisms from blood cultures; the isolation of organisms from urine (*Candida*) or respiratory cultures (*Candida* and sometimes *Aspergillus*) may reflect colonization rather than infection in certain circumstances (81,94). Further complicating diagnostic confirmation is the slow growth of some fungi in cultures, a factor that may substantially delay the diagnosis. Urine, serum, and cerebrospinal antigen assays have reasonable sensitivity for some organisms (including *Histoplasma*, *Blastomyces*, and *Cryptococcus*) (95,96). It is more difficult to diagnose other fungal infections noninvasively; serum

galactomannan and β -D glucan assays may provide clues to the presence of a fungal infection but have not been extensively validated in transplant recipients; thus, they cannot be viewed as definitive. Because the lungs are a common site of infection, chest radiography, especially computed tomography, may provide important clues to diagnosis. Ultimately, invasive procedures, including tissue biopsy, in conjunction with culture remain the gold standard for confirming the diagnosis of fungal infection.

Treatment of fungal infections may be complicated by drug interactions and the potential for immune reconstitution syndromes with immunosuppression reduction, especially in patients with cryptococcal infection (82,96). The choice of antifungal should reflect the expected pathogen and site of infection (see earlier discussion of UTIs) and consider the potential for drug interactions. If azoles are used for treatment, the calcineurin inhibitor dose should be pre-emptively reduced at the time of azole initiation, typically by at least 50%, although greater reductions will be required for voriconazole (82). Voriconazole and sirolimus should not be administered concurrently because of the marked increase in sirolimus levels with the addition of voriconazole (82). Given the complexity of treating these infections, infectious diseases consultation is recommended.

Limited data support the routine use of antifungal prophylaxis in kidney transplant recipients. However, KDIGO guidelines recommend oral and esophageal candida prophylaxis with oral clotrimazole lozenges, nystatin, or fluconazole for 1–3 months after transplantation or a month after antilymphocyte antibody therapy (5). Transplant candidates with a history of fungal infection should be evaluated by an infectious disease expert before transplantation to determine whether the patient needs additional prophylaxis after transplantation.

Conclusion

Although infections remain a significant cause of morbidity and mortality after transplantation, improved prophylactic, diagnostic, and treatment strategies have decreased the negative effect of infection on transplant outcomes. Ongoing attention to infection prevention beginning before transplantation as well as improved surveillance for infections should be maintained in all patients being considered for transplantation.

Disclosures

E.A.B. is a member of the Data and Safety Monitoring Board for Pfizer and Chimerix; and on the Event Adjudication Committee for Novartis.

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