

## Long-Term Infectious Complications of Kidney Transplantation

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### Abstract

Infections remain a common complication of solid-organ transplantation. Most infections in the first month after transplant are typically health care–associated infections, whereas late infections, beyond 6–12 months, are community-acquired infections. Opportunistic infections most frequently present in the first 12 months post-transplant and can be modulated on prior exposures and use of prophylaxis. In this review, we summarize the current epidemiology of postkidney transplant infections with a focus on key viral (BK polyomavirus, cytomegalovirus, Epstein-Barr virus, and norovirus), bacterial (urinary tract infections and *Clostridioides difficile* colitis), and fungal infections. Current guidelines for safe living post-transplant are also summarized. Literature supporting prophylaxis and vaccination is also provided.

CJASN 17: ●●●–●●●, 2022. doi: <https://doi.org/10.2215/CJN.15971020>

### Introduction

The field of transplantation has been transformed since the first kidney transplant was performed (1). Significant advances in surgical technique and induction and maintenance immunosuppression regimens have improved allograft outcomes. Nonetheless, infections remain a leading cause of complications after kidney transplantation (2,3). Over time, the field of transplant infectious diseases has grown, and discovery and implementation of modern antimicrobial prophylaxis has contributed to delaying and reducing the incidence of post-transplant infections (3). This review summarizes the timing of infectious complications and discusses common post-transplant infections and tactics to minimize infectious risk, as well as approaches to safe living.

### Timing of Infectious Complications in Kidney Transplantation

Infectious complications are categorized as occurring in one of three time periods post-transplant: early post-transplant infections, infections during peak immunosuppression, and late-onset infections (Figure 1) (3,4). A number of factors affect the timing of the infections, including specific donor and recipient factors such as a pre-existing infection or immunity, the use of antimicrobial prophylaxis, and the net state of immunosuppression. Of these, the net state of immunosuppression is harder to assess because there are no direct measures. Instead, the clinician must assess a variety of factors, including current and past immunosuppression; underlying immunodeficiency; neutropenia; lymphopenia; a variety of complex metabolic conditions, such as presence of uremia, malnutrition, poorly controlled diabetes mellitus, and cirrhosis; and replication of immunomodulatory viruses. Net state of immunosuppression not only reflects the medications

the patient is currently taking, but also agents, such as alemtuzumab or rituximab, which may be used as part of induction or in the treatment of rejection and may have longstanding effects on components of the immune system. Further, recent changes in immunosuppression may alter the assessment of the net state of immunosuppression. Taken together, these considerations allow a clinician to estimate if the patient is more or less immunosuppressed than the usual patient.

Early post-transplant infections are infections that occur in the first 30 days post-transplant (5). The majority of such infections (approximately 98%) are common post-surgical infections, including surgical site infections, pneumonias, urinary tract infections (UTIs), bacteremias, and *Clostridioides difficile* colitis. Management approaches for such infections are consistent with the local epidemiology and susceptibility of predicted pathogens and published guidelines (5).

Recipient-origin infections may manifest in the first 30 days. Examples of recipient-origin infections include respiratory viral infections or occult bacteremias that were incubating in the candidates at the time they present for their transplant procedures.

Donor-derived infections, although rare (approximately 0.2%), may present during the first 30 days post-transplant (6). Donor-derived infections are defined as any infection present in the donor that is transmitted to the recipient with the transplanted organ or vessels (6–9). Such infections can be categorized as either expected, where the pathogen is known to be present in the donor at the time of procurement regardless of whether steps are taken to mitigate the disease transmission (*e.g.*, cytomegalovirus [CMV] and Epstein-Barr virus [EBV]), or unexpected, when the donor infection is not recognized and is identified after clinical disease presents in one or more of the transplant

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Early Post-Transplant Infections 0–30 Days Post-Transplant	Period of Peak Immunosuppression 31–365 Days Post-Transplant	Late-Onset Infections >365 Days Post-Transplant
<p><b>Nosocomial Infections</b></p> <ul style="list-style-type: none"> <li>• MDRO: MRSA, VRE, ESLB/CRE</li> <li>• <i>C. difficile</i> colitis</li> <li>• Surgical site infections</li> <li>• Urinary tract infection</li> <li>• Catheter-related bloodstream infections</li> <li>• Pneumonia</li> </ul> <p><b>Donor-Derived Infections</b></p> <ul style="list-style-type: none"> <li>• Atypical post-transplant course</li> <li>-Examples: LCMV, WNV, <i>T. cruzi</i>, HCV, Bacteremia, endemic mycoses</li> </ul> <p><b>Recipient-Derived Infections</b></p> <ul style="list-style-type: none"> <li>• Incubating or colonizing</li> <li>-Influenza, <i>Pseudomonas</i>, <i>Aspergillus</i></li> </ul>	<p><b>With Prophylaxis</b></p> <ul style="list-style-type: none"> <li>• Polyomaviruses</li> <li>• HCV</li> <li>• <i>Cryptococcus neoformans</i></li> <li>• <i>M. tuberculosis</i></li> <li>• Strongyloides</li> <li>• Leishmania</li> <li>• PTLD</li> </ul> <p><b>After Prophylaxis Stops</b></p> <ul style="list-style-type: none"> <li>• Pneumocystis</li> <li>• Herpesviruses (CMV, HSV, VZV)</li> <li>• HBV</li> <li>• Listeria, Nocardia, Toxoplasmosis</li> <li>• Community-Acquired Infections</li> <li>-Urinary tract infection</li> <li>-Pneumonia</li> <li>-<i>C. difficile</i> colitis</li> </ul>	<p><b>Opportunistic Infections</b></p> <ul style="list-style-type: none"> <li>• When these occur, must consider why they are happening late</li> <li>• CMV</li> <li>• JC/PML</li> <li>• PTLD/EBV</li> <li>• Nocardia</li> </ul> <p><b>Community-Acquired Infections</b></p> <ul style="list-style-type: none"> <li>• West Nile Virus</li> <li>• Community-acquired Pneumonia</li> <li>• Urinary tract infections</li> <li>• Influenza</li> <li>• <i>Aspergillus</i>, atypical molds</li> <li>• Hepatitis B or C</li> </ul>

**Figure 1. | Common infections associated with time since kidney transplantation.** *C. difficile*, *Clostridioides difficile*; CMV, cytomegalovirus; EBV, Epstein-Barr virus; ESLB/CRE, extended spectrum beta-lactamase/carbapenem resistant enterobacteria; HBV, hepatitis B virus; HCV, hepatitis C virus; HSV, herpes simplex virus; JC/PML, JC virus/progressive multifocal leukoencephalopathy; LCMV, lymphocytic choriomeningitis virus; MDRO, multi-drug resistant organism; MRSA, methicillin-resistant *Staphylococcus aureus*; *M. tuberculosis*, mycobacterium tuberculosis; PTLD, post-transplant lymphoproliferative disease; *T. cruzi*, *Trypanosoma cruzi*; VRE, vancomycin-resistant enterococcus; VZV, varicella zoster virus; WNV, West Nile virus.

recipients. Most (76%) unexpected donor-derived infections present within 30 days of transplantation (6).

Clinicians should have a high index of suspicion for donor-derived infections in any patient with atypical early post-transplant course, unexplained sepsis, fever, or alteration in mental status in the first 30–45 days post-transplant. Those with early infections should always prompt review of donor cultures and history. Recognition and reporting of potential donor-derived infections are essential because they may potentially affect all of the recipients of organs from the same donor. In the United States, any documented or suspected unexpected donor-derived disease transmissions need to be reported to the Organ Procurement and Transplantation Network (OPTN) as soon as possible, but not >24 hours after initially suspecting transmission (OPTN Policy 15.4), through the Patient Safety Portal. Timely reporting of suspected transmissions is essential to facilitate communication and rapidly allow screening and treatment of recipients of organs from the same donor (10).

The second period of post-transplant infections occurring during peak immunosuppression are typically opportunistic infections or pathogens that reactivate from latent infection in the recipient, such as BK virus, CMV, herpes simplex virus (HSV), varicella zoster virus, hepatitis B virus, hepatitis C virus (HCV), tuberculosis, listeria, strongyloidiasis, and Chagas disease, and generally occur between 30 days and 6 months post-transplant or within 3 months of treatment of rejection. Patients with potent induction therapy, particularly those with persistent lymphopenia, have an extended period of risk (3,4). Use of prophylactic antimicrobials may delay the infection onset, resulting in later than typical onset.

Late-onset infections typically present >6–12 months post-transplant, or >3 months after treatment for a rejection episode

(3,4). Most late-onset infections are community acquired, such as community-acquired pneumonia, respiratory viral infections, and UTIs. Patients may acquire infections from exposure to the environment or travel, which increases over time as the patient returns to normal function. Patients may also become less cautious, which can lead to a higher risk of community-acquired infections, as we have seen with coronavirus disease 2019 (COVID-19) (11). Rarely, opportunistic infections may present in this late period, including progressive multifocal leukoencephalopathy or *Pneumocystis jirovecii* (12).

### Viral Infections

Although the remainder of this virology review will focus on some of the more common viral infections complicating kidney transplant, there are others that warrant discussion but already have excellent recent reviews. For example, there is a growing body of literature about HCV in kidney transplantation. Most patients are treated before transplantation, making post-transplant HCV management a rare issue, with the exception of intentional transmission of HCV from nucleic acid test-positive donors (13). Recent studies suggest the ability to treat HCV in this setting, with shorter course of therapy, but optimal approaches are yet to be defined (14).

Respiratory viral infections, including influenza, respiratory syncytial virus, and COVID-19, can result in severe infections in kidney transplant recipients, but frequently are self-limited (15). Vaccines for influenza are recommended in all transplant recipients and their close contacts. Antiviral therapy with neuraminidase inhibitors are recommended for the treatment of influenza in kidney transplant recipients; baloxavir marboxil, a new anti-influenza antiviral, is approved but generally not recommended for

transplant recipients because of the concern for emergence of resistance. Although the optimal therapy for COVID-19 has yet to be defined for kidney transplant recipients, most current guidelines recommend considering remdesivir, dexamethasone, and/or convalescent plasma (11).

### Epstein-Barr Virus

EBV is a human herpesvirus infecting about 90% of adults. It is transmitted mainly *via* oropharyngeal secretions, and primary infection is commonly asymptomatic. EBV remains latent within the B lymphocytes, but can reactivate post-transplant. This can manifest as asymptomatic viremia, infectious mononucleosis syndrome, or other organ involvement such as hepatitis, myocarditis, and pancreatitis. The majority of symptomatic infections in kidney transplant recipients are primary infection, likely related to reactivation of donor virus. The most concerning presentation of EBV is post-transplant lymphoproliferative disorder (PTLD) (16,17).

Current guidelines recommend routine screening for EBV in high-risk kidney transplant recipients (donor EBV seropositive [D+]/recipient EBV seronegative [R-]) by nucleic acid testing (18). Monitoring is performed at regular intervals in the first year post-transplant, and after treatment of acute rejection. Reduction of immunosuppression should be considered in EBV-naïve recipients with an increasing EBV viral load (19). Subclinical EBV DNAemia has been reported in up to 40% of patients in the first post-transplant year and is associated with worse graft outcomes and increased opportunistic infections (20).

PTLD represents 21% of all cancers in solid-organ transplants recipients (21,22). Early-onset PTLD, occurring within the first post-transplant year, is commonly seen in younger individuals and is more frequently associated with EBV positivity and allograft involvement (22). The most common risk factors for PTLD are EBV D+/R- status and the degree of immunosuppression, with T cell-depleting induction a strong factor. A recent meta-analysis concluded that antiviral prophylaxis had no effect on PTLD incidence (23). Belatacept, a costimulation blocker approved in kidney transplant recipients, is contraindicated in EBV-seronegative recipients because of an estimated ten-fold higher risk of PTLD reported during the phase 3 studies (24,25). If there is a clinical suspicion of PTLD, the quantitative blood EBV viral load should be assessed, although there are no specific diagnostic levels.

The cornerstone of EBV/PTLD management is immunosuppression reduction, which leads to disease regression in 20%–80% of cases. PTLD management should be done in consultation with an oncologist, who may recommend anti-B cell therapy (rituximab), chemotherapy, and/or radiation. Adoptive immunotherapy with EBV-specific T lymphocytes is an emerging therapeutic option (26). In the largest series of patients retransplanted after PTLD, only one of the 52 patients developed recurrent PTLD (27).

### Cytomegalovirus

CMV is a ubiquitous human herpesvirus, with a seroprevalence rate of 30%–97% (28,29). The risk of CMV infection or disease after transplant is determined primarily by the donor and recipient CMV serostatus (from highest to

lowest risk: D+/R-, D+/R+, D-/R+, D-/R-) (29). Use of lymphocyte-depleting agents, as induction or for allograft rejection, has been shown to significantly increase the risk of CMV disease (28,29). Of the newer immunosuppressive agents, belatacept has been associated with an increased risk of CMV primary infection and a prolonged course of viral replication in patients at high risk of CMV (30). In the absence of preventive measures, CMV infection and disease develop in 40%–100% and 67% in kidney transplant recipients, respectively. With the current preventive strategies, the incidence is about 17%–37%, with the highest risk in the first 100 days (28,29).

Immune monitoring of CMV-specific T cell responses is another strategy to assess post-transplant CMV risk. IFN- $\gamma$  release assays (QuantiFERON-CMV, ELISpot) and intracellular cytokine staining for IFN- $\gamma$  have been shown to predict both CMV viremia and disease (31). Emerging data suggest that detection of CMV-specific immunity is associated with a lower risk of infection and may be helpful in determining duration of prophylaxis and preemptive monitoring (28).

The key strategies for prevention of CMV are universal prophylaxis, preemptive therapy, and a hybrid approach known as “surveillance after prophylaxis” (29). There are data to support each strategy, and current guidelines suggest any approach is acceptable. Prophylaxis is easier in the outpatient setting, protects against HSV and varicella zoster virus, and is associated with rare instances of early CMV infection and lower rates of graft rejection. It is, however, associated with risk of late-onset CMV, resistance development, higher drug costs, and side effects. In a single-center study of 176 patients with CMV D+/R-serostatus, 29% of patients developed CMV disease at a median of 61 days after stopping antiviral prophylaxis (32). Preemptive therapy lacks some of the benefits listed above, but results in lower rates of late-onset CMV and less drug toxicity. Preemptive therapy has higher laboratory costs and has also been associated with resistance development.

Oral valganciclovir is the most commonly used prophylaxis medication, with a recommended dose of 900 mg daily, and dose reduction for kidney dysfunction (28,29). Most guidelines recommend 100 days of prophylaxis for intermediate-risk patients and 200 days of prophylaxis for high-risk patients (33). Letermovir, a novel viral terminase inhibitor, is being evaluated for prophylaxis in CMV D+/R- kidney recipients, but does not have HSV coverage. Patients with CMV D-/R- serostatus have a very low risk of CMV disease, and acyclovir prophylaxis can be used to prevent HSV (29).

CMV can present as asymptomatic DNAemia, CMV syndrome (viremia, constitutional symptoms, cytopenias without organ involvement), or tissue invasive disease. CMV disease can affect many organs; most commonly, the gastrointestinal tract, liver, pancreas, and lung. CMV also has a predilection to cause allograft nephritis. CMV has been described to have immunomodulatory effects and can increase risk of activation of other herpes viruses, EBV-mediated PTLD, allograft rejection, and other opportunistic infections. CMV infection and disease have been associated with higher risk of mortality and graft loss (34).

All patients with a clinical suspicion for CMV infection or disease should be tested by PCR of blood or serum, which

are less sensitive for certain organ-invasive diseases like gastrointestinal disease and retinitis (35). Histopathologic examination of tissue biopsy specimens may be needed to diagnose invasive CMV disease (36).

CMV management involves immunosuppression reduction and antiviral therapy. Antimetabolites may be stopped or reduced, depending upon the immunologic profile of the recipient. First-line therapy for CMV is valganciclovir or intravenous ganciclovir. Intravenous therapy is preferred in life-threatening illness, CMV pneumonitis, and colitis. Both agents require monitoring of blood counts and kidney function, with dose reduction for kidney dysfunction. Treatment is continued until there is clinical improvement and CMV viral loads are undetectable. Although secondary prophylaxis has previously been widely used, recent data suggest it may not be required for most patients (28,29). Genotypic assays for resistance should be performed if DNAemia persists despite 2 weeks of antiviral therapy (37). Second-line agents used for treatment of resistant CMV include foscarnet, high-dose ganciclovir, cidofovir, and CMV Ig. Letermovir is not approved for CMV treatment. Off-label use for ganciclovir-resistant CMV has been complicated by emergence of the letermovir-resistant virus (38). Adoptive transfer of CMV-specific T cells may be considered as adjunctive therapies for resistant CMV, in collaboration with transplant infectious disease experts (29).

### Polyomaviruses

The BK polyomavirus is a human polyomavirus, first identified in the urine of a kidney transplant recipient with ureteral stenosis (39). Primary BK polyomavirus infection occurs during childhood, with 80%–90% adults being exposed (40). The virus remains latent in the kidney tubules and uroepithelium (41).

In immunocompromised hosts, the disease can progress from asymptomatic viruria to viremia and organ-invasive disease. It usually presents as BK polyomavirus-associated nephropathy in kidney transplant recipients (42). Asymptomatic viruria, detected on routine screening, is the earliest manifestation and is seen in 25%–40% of patients in the first year. Of those with persistent viruria and high urinary viral loads, 10%–20% develop viremia after a few weeks. BK polyomavirus-associated nephropathy occurs in patients with persistent high-titer viremia, typically >10,000 copies/ml, and is seen in 1%–10% of all kidney transplant recipients (40,43). It most commonly occurs in the first post-transplant year, when the degree of immunosuppression is the highest. The most significant risk is the degree of immunosuppression, but other factors are donor related (viruria, female sex, deceased donor), recipient related (male sex, highly sensitized status, ABO incompatibility, HLA mismatch, low BK polyomavirus-specific neutralizing antibody or T cell activity), or transplant related (ureteric stent, treatment for acute rejection, tacrolimus exposure) (40,44).

Current guidelines recommend routine post-transplant screening for BK viremia monthly for 9 months, and then every 3 months until 2 years' post-transplant. Screening is also recommended when evaluating for graft dysfunction and with a kidney allograft biopsy (40). Early detection of BK polyoma viremia combined with reduction in immunosuppression can

prevent progression to BK polyomavirus-associated nephropathy and preserve graft function (45).

Viremia has a 50%–60% positive predictive value for diagnosis of BK polyomavirus-associated nephropathy, and patients with sustained viral loads of  $\geq 10,000$  copies/ml are presumed to have BK polyomavirus-associated nephropathy (40,43). Kidney biopsy is the gold standard for diagnosis and is helpful in assessing disease severity, chronicity, and concurrent rejection. Given the patchy involvement of the kidney, guidelines recommend two biopsy cores containing medulla and immunohistochemistry for SV40 T antigen (46).

The cornerstone of management of BK viremia and nephropathy is immunosuppression reduction (45). The various strategies for reduction have not been compared in randomized controlled trials, and center-specific, individualized protocols are used. Worsening kidney allograft function after reduction of immunosuppression should prompt evaluation for possible graft rejection with a biopsy (19). Acute rejection has been reported in 8%–12% after reduction of immunosuppression for BK viremia or nephropathy (45,47). In a retrospective cohort of patients with BK polyomavirus-associated nephropathy, 14% developed *de novo* donor-specific antibodies, which was a risk factor for subsequent antibody-mediated rejection and graft loss (48).

Other adjunctive treatments used with varying degree of success include intravenous Ig, leflunomide, and cidofovir (40). Data from randomized controlled trials do not demonstrate superiority of one or more of these therapies over immunosuppression reduction alone (49). Intravenous IG may be considered in patients with severe hypogammaglobulinemia, concomitant rejection, or those at high immunologic risk. Leflunomide has both immunosuppressive and antiviral activity and has been used to replace the antimetabolites in recipients with a higher risk of rejection. It is, however, associated with hematologic and hepatotoxicity, and therapeutic drug monitoring is difficult (50). Cidofovir is associated with a dose-dependent nephrotoxicity, and its use is not recommended in patients with significant kidney dysfunction or proteinuria. Quinolones are no longer recommended for treatment of BK polyomavirus-associated nephropathy (51). Adoptive T cell therapy is a novel therapeutic option in BK polyomavirus-associated nephropathy and has been shown to reduce viral load in the kidney tubules when used early in the course of the disease (52).

Unfortunately, graft loss occurs in 15%–50% of BK polyomavirus-associated nephropathy cases. Retransplantation in these patients has been successful, with 5-year death-censored graft survival of 90.6% (53). Undetectable levels of viremia at time of retransplantation were associated with absence of BK viremia at 1 year post-transplant. In patients with persistent viremia, a decline of at least 2  $\log^{10}$  copies/ml after reduction of immunosuppression indicates an antiviral immune response, and retransplant maybe considered (54). The role of transplant nephrectomy before a second transplant is not well defined, but can be considered in those with persistent viremia (55).

### Norovirus

Norovirus infections typically present as an acute infection characterized by severe nausea; vomiting; watery,

nonbloody diarrhea; abdominal cramps; and occasionally, low-grade fever, muscle aches, chills, and headache in immunocompetent hosts (56). Immunocompromised patients can develop chronic norovirus infections, associated with relapsing and remitting episodes of watery diarrhea that may last for months to years (57). Norovirus is the second most common documented cause of diarrhea, after *C. difficile*, among solid-organ transplant recipients (58). A total of 30% of patients with chronic norovirus have a  $\geq 20\%$  increase in creatinine within 1 year of the diagnosis, as a result of recurrent dehydration and suprathreshold tacrolimus levels during periods of diarrhea (58). Given the high prevalence of norovirus, kidney transplant recipients with diarrhea, particularly chronic or relapsing diarrhea, should be screened for norovirus by PCR or antigen testing of stool (59).

The current mainstay of therapy for norovirus is supportive, with antimotility agents and hydration (57–59). Reduction of immunosuppression is commonly practiced, although there is no clear evidence that it is associated with viral clearance (57). Several agents, including oral and intravenous Igs and nitazoxanide, are used off-label, with variable evidence to support their use, and a clinical trial of nitazoxanide is ongoing (57).

## Bacterial Infections

### *Clostridioides difficile*

*C. (formerly Clostridium) difficile*, an anaerobic, spore-forming, Gram-positive bacterium, causes *C. difficile* infection, which is five times more likely in hospitalized solid-organ transplant recipients compared with the general population (60). *C. difficile* infection affects 3%–16% of kidney transplant recipients, often early post-transplant (60,61). Severe presentation with fulminant colitis (5.3%) and need for colectomy (2.7%) appear to be higher than in other patient populations, and *C. difficile* infection has been associated with graft loss in at least one study (61,62). Recurrences of *C. difficile* infection have been reported in nearly 20% of solid-organ transplant recipients, comparable with other hospitalized patients (62). Risk factors for *C. difficile* infection include those reported in nontransplant patients such as recent antibiotic exposure, age  $> 65$  years, acid suppression medications, and hospitalization (60). Additionally, transplant-specific risks include induction with antithymocyte globulin and hypogammaglobulinemia (60,63). Diagnosis relies on presence of three or more unformed stools in a 24-hour period, and the demonstration of *C. difficile* toxin or PCR testing of the stool. Unexplained abdominal pain with fever and leukocytosis in a patient with ileus should prompt *C. difficile* infection testing (60). Primary therapy with oral vancomycin or fidaxomicin is suggested for both severe and nonsevere events (60,64). High-dose oral vancomycin with intravenous metronidazole is recommended for fulminant cases, with consideration for surgical intervention (60,64). In addition, bezlotoxumab, a human mAb against toxin B, can be considered in solid-organ transplant recipients at higher risk for recurrence of *C. difficile* infection (60,65). For recurrences, treatment options include either fidaxomicin or prolonged, tapered, or pulsed oral vancomycin (64). Additionally, fecal microbiota transplantation should be

considered with multiple recurrences and has been shown to be safe and potentially helpful in some, but not all, solid-organ transplant recipients (66).

### Urinary Tract Infection

UTIs are the most common infections in kidney transplant recipients. They occur most commonly in the first year post-transplant, with a prevalence that ranges widely from 7%–80% (67). Similar to nontransplant patients, the incidence of UTIs is higher in female kidney transplant recipients because of anatomic predisposition (68). Gram-negative bacteria cause up to 90% of cases, and *Escherichia coli* was most commonly reported (69).

Perioperative and prophylactic antibiotics during the early post-transplant period are standard-of-care measures adopted to prevent UTIs. Trimethoprim-sulfamethoxazole is recommended for 6–12 months post-transplant to prevent *P. jirovecii* pneumonia, but it also serves as an effective UTI prophylaxis and lowers the risk of both UTI and bacteremia (12). Current guidelines recommend that patients who cannot take trimethoprim-sulfamethoxazole for prophylaxis receive an additional antibiotic for UTI prevention, at least until the ureteral stent is removed (70). Minimizing the stent duration is associated with the lowest risk of early post-transplant UTIs, but needs to be balanced against risk of urological complications (71).

Postkidney transplant UTIs can be categorized as asymptomatic bacteriuria, uncomplicated UTI/simple cystitis, complicated UTI/pyelonephritis, or recurrent UTI. Asymptomatic bacteriuria is diagnosed by a screening urine culture without concurrent symptoms. Although it was once thought to be associated with complications, recent data suggest that there is no benefit in treating asymptomatic bacteriuria, with treatment associated with risks of adverse events, including *C. difficile* infection (72). Current guidelines recommend against surveillance urine cultures or treating asymptomatic bacteriuria in most kidney transplant recipients. However, if two consecutive urine samples yield  $> 10^5$  of the same uropathogen in the first 2 months post-transplant, antibiotic treatment for 5 days may be considered (70).

Uncomplicated UTIs are diagnosed in patients with lower urinary tract symptoms and a positive urine culture. Transplant recipients with clinical symptoms of cystitis can be treated with oral antibiotics based on the organism isolated for 5–7 days (70). Complicated UTIs present with systemic symptoms (fever, chills, malaise, nausea, vomiting) and/or allograft pain with a positive urine culture. Bacteremia may be present in approximately 10% of cases. Urine and blood cultures should be collected before initiation of therapy, and imaging of the urinary tract should be obtained. Management includes empirical broad-spectrum parenteral antibiotics, which can be narrowed to definitive treatment once the organism and susceptibilities are identified. Patients can be switched to oral antibiotics once the clinical condition improves, to complete a 7–14 day course (70).

Recurrent UTIs are defined as three or more episodes in 1 year, or two or more episodes in 6 months. Urinary tract obstruction owing to strictures or calculi, indwelling urinary stents, complex kidney cysts, vesico-ureteric reflux,

and bladder dysfunction can result in recurrent UTIs. Suppressing antibiotic prophylaxis has limited efficacy in kidney transplant recipients (73) and poses risk of emergence of drug-resistant organisms. Methenamine hippurate has been shown to reduce frequency of UTIs, antibiotic use, and need for hospitalization in kidney transplant recipients (74,75). Although strong evidence is lacking, strategies such as behavioral education (perineal hygiene, postcoital voiding in women, frequent voiding), *Lactobacillus* probiotics, d-mannose, cranberry products, and vaginal estrogens and hyaluronic acid/chondroitin sulfate in postmenopausal women can also be tried (70).

UTIs caused by drug-resistant organisms, such as extended-spectrum  $\beta$ -lactamase-producing Gram-negative bacteria and carbapenem-resistant Enterobacteriaceae, are increasing in kidney transplant recipients. Intravenous antibiotics are frequently required, namely, carbapenems for extended-spectrum  $\beta$ -lactamase organisms and amikacin and colistin for carbapenem-resistant Enterobacteriaceae. Fosfomycin and nitrofurantoin are the oral agents that retain broad-spectrum antimicrobial activity, and can be used judiciously in patients with cystitis (67). Data regarding the effect of UTIs on patient and graft outcomes are conflicting. Although some studies have shown a higher risk of mortality and graft loss (up to 41% and 29% in the first year, respectively), others have not found an effect on long-term graft function and survival (76–78).

### Fungal Infections

As time from transplant increases, the risk of fungal pathogens associated with early post-operative infections, such as the *Candida* species, can be supplanted by more indolent infections with endemic mycoses, such as histoplasmosis, blastomycosis, and coccidioidomycosis. *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Coccidioides immitis*, and *Coccidioides posadasii* are all dimorphic fungi that exist as yeast in the human body and mycelial forms in the environment. Each pathogen has regional endemicity, which emphasizes the need for local residence and travel evaluation to assess risk. Histoplasmosis and blastomycosis infections are endemic to the upper Midwest of the United States, around the Great Lakes (*Histoplasma*) and the Ohio and Mississippi River valleys (*Histoplasma/Blastomycosis*), whereas *Coccidioides* is predominant in the Southwest United States (79).

Among the endemic mycoses in solid-organ transplant recipients, histoplasmosis is most frequent, causing 5%–9%

of post-transplant invasive fungal infections when early infections with *Aspergillus* and *Candida* are included (80,81). Histoplasmosis occurs in 0.1%–0.3% of kidney transplant recipients, at median of 2–5 years post-transplant (81–83). The most common presentation in kidney transplant includes pneumonia and disseminated disease, but rare presentations occur with cutaneous lesions and hemophagocytic lymphohistocytosis (82–85). Risk factors included leukopenia, CMV, and a diagnosis of bacterial pneumonia (81). One series reported 21% graft failure and 7% (one of 14) mortality (82). Diagnosis focuses on direct visualization or culture from sputum, bronchoalveolar lavage (BAL), or tissue. Noninvasive measures include histoplasma antigen enzyme immunoassay (EIA) from both urine and serum in suspected cases, and serology is of limited assistance (79). Post-transplant prophylaxis is not recommended, and treatment most frequently includes amphotericin, itraconazole, and, more recently, voriconazole and posaconazole (79,83,86). Monitoring histoplasma antigen EIA, particularly in the blood, to assess recovery is suggested by some experts (79).

Blastomycosis is less common overall (80), occurring at a median of 2 years post-transplant (82). Pneumonia has been reported in 80% of kidney transplant with blastomycosis, and disseminated disease commonly includes cutaneous manifestations (82). Risk for blastomycosis in kidney transplant is difficult to assess outside of environmental exposure given the relatively infrequent events; one study from Wisconsin identified two of three cases developed in a minority population, the Hmong (87). Similar to histoplasmosis, diagnosis focuses on direct visualization or culture from sputum, BAL, or tissue. Blastomycosis antigen EIA from urine, serum, BAL, or cerebrospinal fluid is available but less sensitive (62%–83%), and suffers from cross-reactivity with other fungi. Again, serology is of limited assistance (79). Treatment with lipid-formulation amphotericin, with transition to azole therapy after initial recovery, is recommended for severe cases, whereas primary azole therapy can be used for mild cases (79).

Coccidioidomycosis caused by *C. immitis* and *C. posadasii* can be donor-derived, newly acquired post-transplant, or a reactivation from prior recipient disease. In endemic regions, 3% of kidney transplant recipients will develop coccidioidomycosis; screening and prophylaxis of high-risk patients reduces infection frequency (79,88,89). Presentation includes cutaneous, skeletal, pulmonary, meningitis, and disseminated disease (89,90). Culture is confirmatory;

**Table 1. Post-transplant vaccination for kidney transplant recipients**

Routine Vaccination	Travel-Related Vaccination
Influenza	Influenza
Hepatitis B	Hepatitis B
Hepatitis A	Hepatitis A
Tdap (diphtheria/tetanus/pertussis)	Tdap (diphtheria/tetanus/pertussis)
<i>Streptococcus pneumoniae</i> (conjugate)	Rabies
<i>Streptococcus pneumoniae</i> (polysaccharide)	Japanese encephalitis
Human papillomavirus	<i>Salmonella typhi</i> (intramuscular, inactivated:
Herpes zoster (varicella, subunit: Shingrix)	typhoid VI polysaccharide vaccine)
Travel-related vaccines should be determined on the basis of anticipated destination, planned activities, prior evidence of seroprotection (hepatitis A virus/hepatitis B virus) and time since prior vaccination (Tdap).	

however, several available serologic assays can provide additional data, especially when used in combination, and may be used for monitoring during recovery (79). Treatment with lipid-formulation amphotericin, with transition to fluconazole therapy after initial recovery, is recommended for severe pulmonary and disseminated cases, whereas primary fluconazole therapy is recommended for meningitis and mild pulmonary disease (79). Lifelong azole suppression is recommended because of the significant risk for relapse in solid-organ transplant recipients.

### Safer Living

Continued health after kidney transplant relies on the identification and mitigation of risk in everyday life. Routine adherence to general infection prevention principles, such as hand washing, is paramount (91). Meticulous care with food preparation, avoidance of undercooked meat, and strict avoidance of well water can lower food-borne pathogen risk. Employment, hobbies, and pet ownership should be discussed. Behaviors that increase risk for sexually transmitted infections should be discussed, and appropriate prevention education and vaccination, such as hepatitis B and age-appropriate human papillomavirus vaccination, should be provided (91–93). Additional focus on vaccine-preventable illness, especially in those increased with travel, should be provided (see Table 1), including annual influenza vaccination, routine adult shingles vaccination, and boosters for tetanus and pertussis (92–94). As many kidney transplant recipients thrive in the post-transplant period, travel for enjoyment may increase. Safety for travel requires evaluation of travel destination, risk assessment dependent on planned activities, and preparation of emergency medication supplies (92). Infection-related risk can be mitigated with pretravel vaccination (*i.e.*, hepatitis A), avoidance of environmental risk (*i.e.*, mosquitos), and preparation for common travel-related diseases (*i.e.*, diarrhea and respiratory infection) (92,93).

### Disclosures

L. Danziger-Isakov reports consultancy agreements with Merck and Takeda; research funding from Ansun Biopharma, Astellas, Merck, Takeda/Shire, and Viracor; participating in a Data Safety and Monitoring Board for Astellas; and served on an advisory board for GlaxoSmithKline. M.G. Ison reports paid consultation from Adagio, AlloVir, Celltrion, Cidara, Genentech/Roche, Janssen, Shionogi, and Viracor Eurofins; research support, paid to Northwestern University, from AiCuris, Janssen, and Shire; honoraria from Adagio, AlloVir, Celltrion, Cidara, Genentech/Roche, Janssen, Shionogi, and Viracor Eurofins; serving as an editor of *American Journal of Transplantation* and *Transplant Infectious Diseases*; and serving as a paid member of Data Safety and Monitoring Boards from Janssen, Merck, SAB Biotherapeutics, Sequiris, Takeda, and Vitaeris. The remaining author has nothing to disclose.

### Funding

None.

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Published online ahead of print. Publication date available at [www.cjasn.org](http://www.cjasn.org).