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Infection in Renal Transplant Recipients

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INTRODUCTION

Infections are a significant cause of morbidity and mortality after kidney transplantation and have been implicated in allograft dysfunction, rejection, and loss. Both opportunistic and traditional organisms are important causes of infection. The risk for specific infections varies with timing posttransplant, exposures, and the degree of immunosuppression. Because the array of pathogens is diverse, the risk factors not necessarily modifiable, and the causative exposures not consistently anticipated, prevention of infection is a complicated and imperfect process. Moreover, the clinical presentation of infection may be atypical in the setting of immunosuppression, making diagnosis more difficult. Concurrent infections with multiple organisms can occur, and in some cases, it is difficult to differentiate infectious from noninfectious causes of patient presentations. Because transplant recipients are chronically maintained on immunosuppression, they are at especial risk for more severe presentations of infection, even with organisms traditionally associated with more benign courses. Prompt and accurate diagnosis is imperative to ensure optimal outcomes.

Infections in kidney transplant recipients can be viewed as the balance of the host interaction with the environment as mediated by prophylactic strategies. Transplant recipients may have underlying conditions associated with depressed host immunity before the administration of the exogenous immunosuppression required to maintain allograft function. The choice of immunosuppression plays an important role in specific infection risks. For example, T-cell depleting therapies, including antithymocyte globulin, increase the risk for opportunistic infection, and mammalian target of rapamycin (mTOR) inhibitors have been associated with skin and soft tissue infections (Table 40.1). The risk for infection also reflects a recipient’s exposures. This includes pretransplant infections that have the potential for latency (e.g., herpesvirus infections, tuberculosis [TB]) as well as infections associated with the transplant including donor-derived and hospital-acquired infections. In the posttransplant setting, new exposures related to environmental and community interactions need to be considered. In some cases, these exposures can be anticipated based on predictive risk periods posttransplant and appropriate prophylaxis can be administered during the highest risk period to reduce the risk for infection; antivirals directed against cytomegalovirus (CMV) are an example of risk mitigation. A thorough evaluation of all potential recipients and donors is critical to manage infection risks.

PRETRANSPLANT RECIPIENT EVALUATION

All potential transplant candidates should undergo screening to identify both active infections that may have an effect on transplant eligibility and latent infections that may reactivate after transplant and affect patient outcomes (Table 40.2). The screening process should include a thorough history of prior infections, environmental exposures associated with infection risks (including current and prior locations of residence, occupations, hobbies, and pets), and close contacts with communicable diseases such as TB. A careful physical
examination should be performed. Laboratory testing should include serological testing for herpesviruses (CMV, herpes simplex virus, varicella zoster virus, and Epstein-Barr virus [EBV]), human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), syphilis, and *Toxoplasma gondii*. In situations where window period infections for HIV, HBV, or HCV may be suspected or if there is concern regarding underlying immunodeficiency that may reduce the sensitivity of serological testing, nucleic acid antibody testing should be obtained. Tuberculin testing is especially important; either interferon gamma release assays (IGRAs) or intradermal tuberculin purified protein

**TABLE 40.1 Common Immunosuppressive Agents and Select Infection Risks**

| Immunosuppressive | Mechanism of Action | Associated Infections |
|-------------------|---------------------|----------------------|
| Alemtuzumab       | Bind to CD52 on lymphocytes, monocytes, macrophages, natural killer cells, and potentially granulocytes to disrupt their function | Opportunistic infections, including bacterial and fungal infections (including PJP), CMV, EBV/PTLD |
| Antithymocyte globulin | Cause lysis of lymphocytes with prolonged lymphocyte depletion | Opportunistic infections, including bacterial, CMV, EBV/PTLD, BK, fungal infection (including PJP, *Cryptococcus*) |
| Basiliximab/Daclizumab | Block IL-2 receptor | Risk for opportunistic infections does not appear to be increased and may be decreased with these agents |
| Belatacept | Disrupt T-cell costimulation and consequently activation | Associated with EBV/PTLD in EBV-seronegative recipients of seropositive organs |
| Tacrolimus | Inhibit cytokine production, primarily IL-2, by CD4-positive T-cells | Possible increase in BK, intracellular pathogens |
| Cyclosporine | Inhibit cytokine production, primarily IL-2, by CD4-positive T-cells | Intracellular pathogens |
| Mycophenolate | Impair T- and B-cell proliferation and function | Early bacterial infections, late CMV, BK |
| Azathioprine | Impair T- and B-cell proliferation and function | Possibly papillomavirus |
| Corticosteroids | Inhibit inflammatory responses and impair T-cell activation | Bacterial pathogens, PJP, Hepatitis B and C |
| Sirolimus/Everolimus | Inhibit cell cycle proliferation | Wound infections, may reduce risk for viral infections |
| Rituximab | Bind to CD20 to disrupt B-cell function | Reactivation of hepatitis B, possible increased risk for PJP |
| Eculizumab | Binds complement protein C5 | Increased risk for meningococcal infection |

*CMV*, Cytomegalovirus; *EBV*, Epstein-Barr virus; *IL*, interleukin; *PJP*, Pneumocystis jirovecii infection; *PTLD*, posttransplant lymphoproliferative disease.

*This includes risk when agents are used for induction or treatment of rejection; the risk may vary based on timing of administration.

**TABLE 40.2 Standard Candidate and Donor Laboratory Screening**

| Organism             | Candidate                  | Donor                  |
|----------------------|----------------------------|------------------------|
| Cytomegalovirus      | Serology                   | Serology               |
| Herpes simplex       | Serology                   | ND                     |
| Epstein-Barr Virus   | Serology                   | Serology               |
| Varicella zoster     | Serology                   | ND                     |
| HIV                  | Serology, NAT if positive serology or risk for window period infection | Serology, NAT if positive serology or risk for window period infection |
| Hepatitis B          | Hepatitis B surface antigen, core antibody, surface antibody; NAT if surface antigen positive, isolated core antibody positive or at risk for window period infection | Hepatitis B surface antigen, core antibody; NAT if surface antigen positive, isolated core antibody positive or at risk for window period infection |
| Hepatitis C          | Serology, NAT if increased risk for infection or unexplained liver enzyme abnormalities | Serology, NAT if increased risk for window period infection |
| West Nile Virus      | Optional for at-risk individuals (seasonal) | Optional for at-risk individuals (seasonal) |
| Treponema pallidum   | Serology                   | Serology               |
| Mycobacterium tuberculosi | Intradermal PPD or interferon gamma release assay | Live donors only |
| Toxoplasmosis        | Serology                   | Serology               |
| Strongyloides stercoralis | Serology for at-risk individuals | Serology for at-risk individuals |
| Trypanosoma cruzi    | Serology for at-risk individuals | Serology for at-risk individuals |
| Coccidioides immitis | Serology for at-risk individuals | Serology for at-risk individuals |
| Histoplasmosis       | Serology for at-risk individuals | Optional serology for at-risk individuals |

*NAT*, Nucleic acid testing; *ND*, not done; *PPD*, purified protein derivative.
TABLE 40.3  Recommended Immunizations for Adult Transplant Candidates and Recipients

| Vaccine                    | Pretransplant          | Posttransplant          | Comments                                                                                                                                                                                                 |
|----------------------------|------------------------|-------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Influenza                  | Annual                 | Annual                  | Posttransplant, may delay immunization to late fall if transplanted in the summer and no local influenza activity. Household contacts should be immunized                                                                 |
| Streptococcus pneumonia    | Conjugate vaccine fol-  | If not given pretransplant, should give posttransplant            | Schedule as per ACIP recommendations*                                                                                                                                                                   |
|                            | lowed by polysaccharide capsule vaccine |                                                                 |                                                                                                                                                                                                       |
| TDAP                       | Give if not previously given | Give if not previously given | Tetanus toxoid should be given every 10 y thereafter                                                                                                                                                  |
| Hepatitis B                | Give high dose on regular schedule to patients without prior history of hepatitis B | Safe to give posttransplant | All patients with ESRD should have response to hepatitis B vaccine assessed after completing series and if not immune, should administer full series again at increased dose |
| Hepatitis A                | Give to individuals at increased risk | Safe to give posttransplant |                                                                                                                                                                                                       |
| HPV                        | Give to eligible individuals | Safe to give posttransplant | Indicated for patients receiving eculizumab                                                                                                                                                           |
| Meningococcal conjugate vaccine | Consider live attenuated or subunit vaccine | Subunit vaccine if not immunized before transplant | Assess before immunization status to determine whether indicated                                                                                                                                        |
| Zoster                     | Inactivated vaccine recom-  | Inactivated vaccine recom-  | Posttransplant and candidates receiving immunosuppression should receive injectable vaccine; oral vaccine acceptable pretransplant. Reimmunization may be indicated for subsequent travel |
| Polio vaccine              | mended for travelers to at-risk countries | mended for travelers to at-risk countries |                                                                                                                                                                                                       |
| Yellow fever vaccine       | For at-risk travelers | For at-risk travelers |                                                                                                                                                                                                       |
| Salmonella typhi           | For at-risk travelers | For at-risk travelers |                                                                                                                                                                                                       |

ACIP, Advisory Committee on Immunization Practices; DTAP, Tetanus, diphtheria, and acellular pertussis; ESRD, end-stage renal disease; HPV, human papillomavirus.

*From Kim DK, Riley LE, Harriman KH, et al. Advisory Committee on Immunization Practices Recommended Immunization Schedule for Adults Aged 19 Years or Older - United States, 2017. MMWR Morb Mortal Wkly Rep. 2017;66(5):136-138.

derivative (PPD) placement can be performed. Since both tests have reduced sensitivity in patients with end-stage renal disease, a detailed history focusing on common risk factors and radiography are important components of this evaluation. For patients with a history of birth or prolonged residency in places where there are increased risks for geographically associated infections (e.g., strongyloidiasis, Chagas disease, coccidioidomycosis, and histoplasmosis), additional serological testing for the specific organism should be considered. During the pretransplant evaluation, immunization histories should be reviewed and vaccines updated as appropriate (see immunization section; Table 40.3).

DONOR EVALUATION

Donor-derived infections occur rarely. Nevertheless, both living and deceased organ donors have been implicated in donor-derived infections; transmissible pathogens are diverse and include bacteria (e.g., pyogenic organisms and Mycobacterium tuberculosis), fungi (especially endemic mycoses and Candida), viruses (most commonly herpesviruses), and parasitical organisms (including strongyloides). Standard evaluations of both should include a thorough history of past infections and exposures associated with transmissible infections. Because deceased donor histories are provided by surrogates, they are generally less detailed; however, the increased use of paired kidney exchange has led to increased numbers of evaluations being obtained outside the recipient’s center. Whether this impacts on the quality of donor information is unknown. In both cases, laboratory testing should mirror that of the transplant candidate with specific attention to active infections at the time of deceased donation and infections that may reactivate in an immuno-suppressed transplant recipient (including herpesviruses, endemic mycoses, and parasitical infections) in both living and deceased donors (see Table 40.2). Live donors may be evaluated for latent TB using either intradermal tuberculin PPD testing or IGRA. Given the limitations of TB testing in the setting of deceased donor evaluation, it is especially important to obtain historical information and radiography to assess the potential for deceased donor latent infection. The presence of potentially transmissible donor infections may not exclude a donor from transplantation. Donors with bacteremia, meningitis, or other bacterial infections that do
not involve the kidney have been successfully used and may be considered, assuming that the donor has been appropriately treated for 24 to 48 hours and there are acceptable antimicrobial treatment options. \(^6\) \(^9\)-\(^11\) Latent infections in the donor including TB and endemic mycoses may be treated with appropriate antimicrobials after transplantation. Donors who are actively infected with organisms that do not have effective treatment options should be excluded. Special attention should be paid to deceased donors with undiagnosed central nervous system (CNS) processes as these donors have been implicated in severe and fatal donor-derived infections, including West Nile Virus, rabies, and Cryptococcus; consequently the risks associated with using these donors must be balanced with the need for transplantation.\(^12\)

Recent publications have focused on donors who pose an increased risk for blood-borne viral disease transmission because of behaviors associated with recent acquisition of HIV and HCV\(^13\) (Table 40.4). Depending on the screening methodology used (serological vs. nucleic acid testing), there is a window of variable duration during which infection may be present but cannot yet be detected. The Public Health Service (PHS) increased risk donor (IRD) criteria attempt to identify donors at risk for window period infections and disease transmission. The absolute risk for disease transmission overall is quite small, but varies based on the risk behavior, the infection in question, and the testing methodology; for example the risk for HIV transmission from a donor who was incarcerated with negative nucleic acid testing (NAT) and antibody testing is 0.9 per 10,000 but the risk for HCV infection from a donor with active intravenous (IV) drug abuse and antibody testing alone is 300 per 10,000.\(^14\)-\(^16\) The prevalence of PHS IRDs is increasing and IV drug users represent the largest proportion of this group of donors.\(^17\)-\(^19\) Compared with deceased donors overall, PHS IRDs are more likely to be young and male and less likely to meet expanded donor criteria\(^20\); despite the better organ quality afforded by these donors, these organs are more likely to be discarded (odds ratio [OR], 0.67; 95% confidence interval [CI], 0.61 to 0.74).\(^20\) However, for recipients who accept these organs, outcomes are equivalent to those observed with non-PHS IRDs.\(^18\),\(^20\)

The updated guidelines and Organ Procurement and Transplantation Network policies require NAT testing for all IRDs as well as specify testing for living donors to be performed within the 28 days before the transplant surgery.\(^13\) There was also greater emphasis placed on the informed consent process for recipients and clarification regarding the assays and intervals for posttransplant testing; recipients of PHS IRDs should have serological and NAT testing for HIV, HBV, and HCV performed between 1 and 3 months after transplant and testing for HBV at 1 year. As the opioid epidemic continues to affect large parts of the United States, and PHS IRDs continue to contribute a substantial number of organs to the donor pool, it is important that patients are counseled about the acceptable posttransplant outcomes as well infectious risks associated with these organ offers, compared with the risk for death and disease transmission on dialysis; in recognition of the high prevalence of HCV infection among the population with end-stage renal disease (ESRD), hemodialysis patients themselves are considered PHS IRDs. It has been shown that patients will consider these organ offers. In one study, younger donor age, exposure to dialysis, and longer wait times for an organ were associated with increased acceptance of PHS IRD.\(^21\)

**TABLE 40.4 The 2013 Criteria for Defining Public Health Service Increased Risk Donors**

| Infection at Risk | Risk Behaviors                                                                 | Time Frame of Risk Behavior |
|-------------------|--------------------------------------------------------------------------------|----------------------------|
| HIV, HCV, HBV     | Persons exchanging sex for money or drugs                                      | Past 12 mo                 |
| HIV, HCV, HBV     | Persons who inject drugs                                                       | Past 12 mo                 |
| HIV, HCV, HBV     | Persons who have been incarcerated for >72 h                                   | Past 12 mo                 |
| HIV, HCV, HBV     | Persons with syphilis, gonorrhea, chlamydia, or genital ulcers                  | Past 12 mo                 |
| HIV, HCV, HBV     | Men who have sex with men                                                       | Past 12 mo                 |
| HIV, HCV, HBV     | Persons having sex with a person with known or suspected HIV, HCV, or HBV      | Past 12 mo                 |
| HIV, HCV, HBV     | Persons having sex with a person who injects drugs                             | Past 12 mo                 |
| HIV, HCV, HBV     | Women who have sex with men who have a history of sex with men                  | Past 12 mo                 |
| HIV, HCV, HBV     | Child <18 mo old born to a mother known or suspected to have HIV, HCV, or HBV  | Past 12 mo                 |
| HIV, HCV, HBV     | Child breastfeeding from a mother known or suspected to have HIV, HCV, or HBV   | Past 12 mo                 |
| HCV               | Persons on hemodialysis                                                        | Past 12 mo                 |

HBV, Hepatitis B virus; HCV, hepatitis C virus.

**TIMELINE OF INFECTION**

Infection risks may be anticipated based on the net state of immunosuppression, patient exposures (defined as active and latent infections in donor and recipient, and healthcare and community environmental and personal contacts), and prophylactic measures (Fig. 40.1). Standard immunosuppression protocols have allowed for the development of a timeline of anticipated infection that provides a starting point for infection assessment\(^1\) (Table 40.5). Infections in transplant patients may be more severe, especially during periods of more intense immunosuppression. They also may be more difficult to recognize due to the absence of typical features of infection (e.g., fever) in patients on immunosuppressive agents, and noninfectious syndromes occasionally mimic infections. Consequently, this timeline should be
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Infection with antimicrobial resistant species:
- MRSA
- VRE
- Candida species (non-albicans)

Aspiration
- Catheter infection
- Wound infection
- Anastomotic leaks and ischemia
- Clostridium difficile colitis

Donor-derived infection (uncommon):
- MRSA
- VRE
- Candida species

Recipient-derived infection (colonization):
- Aspergillus, pseudomonas
- Donor-derived infection (uncommon):
  - HSV, LCMV, rabies, West Nile virus, HIV, Trypanosoma cruzi
- With PCP and antiviral (CMV, HBV) prophylaxis:
  - Polymavirus BK infection
  - C. difficile colitis
  - HCV infection
  - Adenovirus infection, influenza
  - Cryptococcus neoformans infection
  - Mycobacterium tuberculosis infection
  - Anastomotic complications
- Without prophylaxis:
  - Pneumocystis infection with herpesviruses
  - HSV, VZV, CMV, EBV
  - HBV infection
  - Infection with Listeria, Nocardia, Toxoplasma, Strongyloides, Leishmania, Trypanosoma cruzi
- Community-acquired pneumonia, urinary tract infection
- Infection with aspergillus, atypical molds, mucor species
- Infection with nocardia, rhodococcus species
- Late viral infections:
  - CMV infection (colitis and retinitis)
  - Hepatitis (HBV, HCV)
  - HSV encephalitis
  - Community-acquired (SARS, West Nile virus infection)
  - JC polyomavirus infection (PML)
  - Skin cancer, lymphoma (PTLD)

Common Infections in Solid-Organ Transplant Recipients

| Days 1–30 | Months 1–6 | >6 Mo |
|-----------|------------|-------|
| **Bacteria** | Hospital acquired, includes surgical site and device related; may involve resistant donor-derived pyogenic organisms | Opportunistic bacteria including
- listeria, nocardia, tuberculosis, and non-tuberculous mycobacteria
- Donor-derived bacteria | Encapsulated organisms, especially sinopulmonary;
- Urinary tract infections;
- Pancreaticobiliary and diverticular-associated infections |
| **Viral** | Herpes simplex
- Healthcare-associated respiratory viruses
- Donor-derived (LCMV, WNV, etc) | CMV
- EBV/PTLD
- Varicella zoster/herpes zoster
- Polymaviruses (especially BK)
- Donor-derived | Community-acquired respiratory viruses
- CMV (delayed onset due to prophylaxis)
- EBV/PTLD (less common after year 1) |
| **Fungal** | Candida
- Donor derived | Molds, especially aspergillus
- Cryptococcus
- PJP if no prophylaxis | Endemic/environmental mycoses
- Cryptococcus |
| **Parasitical/Protozoal** | Donor derived (e.g., balamuthia) | Strongyloides
- Toxoplasmosis
- Trypanosoma cruzi | Variable risk based on exposures |

CMV, Cytomegalovirus; EBV, Epsterin-Barr virus; LCMV, latent cytomegalovirus; PTLD, posttransplant lymphoproliferative disease; WNV, West Nile Virus.

*Timing presumes no rejection and limited prophylaxis. For patients who are treated for rejection, risk for opportunistic pathogens increases. Prophylactic interventions may delay the onset of opportunistic infections. New exposures (e.g., environmental) may affect timing of infection.
regarded as a starting point and individual patient circumstances should be carefully considered to determine the optimal patient evaluation.

**The Early Posttransplant Period (Month 0 to 1)**

Although immunosuppressive therapies are initiated at maximal doses at the time of transplant, the early posttransplant period is notable for hospital-acquired infections, especially related to the surgical procedure and the use of devices that disrupt the host’s mucocutaneous barriers, including IV and urinary tract catheters. Bacterial infections are most common and given the antibiotic exposure in the peri- and peritransplant period, multidrug-resistant organisms and *Clostridium difficile* have been increasingly implicated in recent years. Donor-derived bacterial infections due to pyogenic organisms are rare but typically also occur in the first month. Fungal infections are less frequently noted; *Candida* species occur most frequently, usually related to devices or less commonly to donor sources. Early viral infections include reactivation of herpes simplex, nosocomial transmission of seasonal respiratory viruses and norovirus, and rarely donor-derived viral infections such as West Nile Virus, rabies, and lymphocytic choriomeningitis virus. It is especially unusual to see parasitical infections in the first month; rare cases of donor-derived infections including *Balamuthia* and *Microsporidia* have been reported.

**Months 1 to 6**

This intermediate period posttransplant is typically considered to be the highest risk period for the occurrence of opportunistic infections. During this time, the effects of exogenous immunosuppression required to prevent rejection are maximal, enhancing the net state of immunosuppression. Further immune modulation may occur in the setting of coinfection with immunomodulating viruses, such as CMV, or related to metabolic derangements (especially diabetes) that are common during this period. Reactivation of latent infections and acquisition of new infections from the environment, other individuals, and the donor may occur; the resulting infections may be more severe in the immunosuppressed host.

The pathogens seen during this intermediate period are diverse and in the absence of prophylaxis, include bacteria (e.g., *Nocardia* species, *Listeria monocytogenes*, and mycobacteria, especially TB), fungi (e.g., *Aspergillus* species, *Cryptococcus*, and *Pneumocystis jirovecii*), viruses (e.g., CMV, EBV), and parasites/protozoa (e.g., toxoplasmosis). Infections with geographically restricted pathogens including *Strongyloides stercoralis*, *Trypanosoma cruzi*, and endemic mycoses (*Coccidioides immitis*, *Blastomyces dermatitidis*, and *Histoplasmosis capsulatum*) also may occur. It is important to recognize that exposures both before and after transplantation may result in infections during this period.

Because some infections may be predictably anticipated, several of the more common opportunistic infections may be prevented by the administration of prophylactic antimicrobials (Table 40.6). The use of trimethoprim sulfamethoxazole to prevent *Pneumocystis jirovecii* pneumonia and valganciclovir to prevent CMV are examples of successful prophylactic strategies. However, prophylactic antimicrobials may not completely eradicate the risk for infection; in some cases, the onset of the disease is merely delayed until after the prophylaxis is discontinued. The changing nature of immunosuppressive strategies and treatment of rejection also may affect the timing and presentation of common opportunistic infections. Consequently, the risk period for opportunistic infections may extend beyond this intermediate risk period.

**Beyond 6 Months**

In stable recipients, the time frame beyond the first 6 months is typically a period of stable allograft function when infections are less frequently noted. Those that occur are typically community acquired infections caused by typical community acquired bacterial and viral infections. Urinary tract infections (UTIs) are especially common and typically caused by *Enterobacteriaceae*, especially *Escherichia coli*. Respiratory tract infections also occur, often due to community-acquired

| Pathogen                  | Antimicrobial              | Duration                  | Comments                                                                 |
|---------------------------|----------------------------|---------------------------|--------------------------------------------------------------------------|
| Cytomegalovirus           | Valganciclovir             | Varies based on risk      | Alternative strategies include valganciclovir for lower risk, monitoring (preemptive therapy) for lower risk (includes CMV D+/R− who do not need valganciclovir) |
| Herpes simplex            | Valacyclovir or Acyclovir  | 3 mo or prolonged if history of HSV recurrences 6–12 mo | Not indicated if patient on valganciclovir Consider longer if patient with increased immunosuppression |
| *Pneumocystis jirovecii*  | Trimehoprim sulfamethoxazole or Atovaquone or Dapsone | 6 mo                       |                                                                           |
| *Candida*                 | Nystatin or Clotrimazole   | 30 d                      | Clotrimazole has been associated with increased calcineurin inhibitor levels |

CMV, Cytomegalovirus; D−, donor negative; D+, donor positive; HSV, herpes simplex virus; R+, recipient-negative.
viruses (influenza, parainfluenza, respiratory syncytial virus, adenovirus, and human metapneumoviruses); these may be more severe with prolonged viral shedding, increased risk for lower tract disease, morbidity, and allograft rejection.\textsuperscript{35-37} Bacterial pathogens including legionella and \textit{Pneumococcus} also occur and transplant patients are at a 12.8-fold greater risk for invasive pneumococcal disease than the general population.\textsuperscript{38,39}

Although this late period is not considered to be a high-risk period for opportunistic infections, some may occur after augmentation of immunosuppression.\textsuperscript{1} It is important to recognize that the net state of immunosuppression cannot be estimated solely by considering the specific medications, doses, and levels; patient responses may vary considerably. Moreover, there are episodes of later rejection that require additional augmentation of immunosuppression and diabetes mellitus, infections, and malignancies may further increase the risk for later opportunistic infections. One of the more common late-onset opportunists is CMV, which usually occurs following suspension of prophylaxis, especially in CMV-seronegative recipients of CMV-seropositive donor organs.\textsuperscript{40} Reactivation of latent infections whose control was dependent on normal T-cell function may occur during this period. For example, histoplasmosis and TB have both been reported; the risk for TB is 20% to 74% higher in transplant recipients than in the general population.\textsuperscript{41-43}

The late period is also notable for the occurrence of healthcare-associated infections. Transplant patients are at increased risk for comorbidities, such as malignancy, diabetes mellitus, and vascular disease, conditions that often require additional interventions in healthcare facilities. These have led to infection with hospital-acquired pathogens, including multidrug-resistant bacteria and \textit{Clostridium difficile}. Diabetic foot infections also may be seen.

**SELECTED INFECTIONS OF IMPORTANCE**

Recognition of infections in the posttransplant period requires consideration of specific recipient and donor exposures, the net state of immunosuppression, comorbidities, and the timing of the infection. Because the list of potential pathogens can be diverse and diagnoses may be obscured in the setting of immunosuppression, broad-spectrum empiric antimicrobial therapy with concurrent detailed evaluation involving laboratory and radiographic evaluations may be necessary to prevent bad outcomes. We provide more in-depth information regarding some of the more common infections encountered after kidney transplantation.

**Cytomegalovirus**

CMV is the most common opportunistic pathogen after kidney transplantation. Notable for both direct and indirect effects, it typically occurs in months 1 to 4 posttransplant if no prophylactic antivirals are administered.\textsuperscript{42} If prophylactic antivirals are used, the onset of infection is delayed until the antiviral is suspended; post-prophylaxis CMV may occur in posttransplant months 6 to 12.\textsuperscript{44} Rarely the onset of CMV is further delayed (late onset), occurring beyond at least 6 months after cessation of prophylaxis.\textsuperscript{44-46} These later infections are differentiated from those occurring shortly after suspension of prophylaxis by their later acquisition, worse allograft function, higher mortality, and absence of association with CMV donor-positive, recipient-negative (D+/R–) serostatus.\textsuperscript{44-46}

The manifestations of CMV are diverse.\textsuperscript{1,40} The most common direct effects are asymptomatic viremia; CMV syndrome, which can include fever, malaise, and cytopenias (usually leukopenia and/or thrombocytopenia); and gastrointestinal (GI) symptoms (including anorexia, diarrhea, abdominal pain, bleeding, ulcerations, and perforation). Disseminated infection, hepatitis, pneumonitis, pancreatitis, and nephritis occur less frequently and chorioretinitis is a rare late manifestation. Of special concern are the indirect manifestations of CMV related to its impact on the host’s immune system; decreased allograft and patient survival, increased risk for rejection, and increased risk for opportunistic infections (including fungal infections), posttransplant lymphoproliferative disease (PTLD), and bacteremia have all been noted.\textsuperscript{47,48} Although the association between CMV and rejection and allograft damage has been recognized for years, the exact mechanism is not known.\textsuperscript{49} Some possible mechanisms include upregulation of the inflammatory response with alterations in the expression of cytokines, proinflammatory growth factors, and chemokines and an increase in proinflammatory adhesion molecules. Increased antigen processing and presentation associated with the major histocompatibility complex (MHC), alterations in the T-cell subset composition, smooth muscle proliferation with induction of intracellular reactive oxygen species, and increased procoagulant activity have been noted.\textsuperscript{47,50,51} Notably administration of antiviral prophylaxis to CMV-seronegative recipients of CMV-seropositive organs has been associated with a 50% reduction in organ rejection and improved patient and allograft survival at 3 years, observations that provide further support for the critical role played by CMV with respect to allograft function.\textsuperscript{52-53}

**Patterns of transmission**

CMV may occur as a result of primary infection, reactivation of latent infection, or superinfection. Primary infection occurs frequently when a CMV-seronegative recipient receives a CMV-seropositive donor kidney with clinically apparent infection in approximately 45% of recipients in the absence of prophylaxis.\textsuperscript{52} Infrequently, primary infection is the result of blood transfusion or close/intimate contact with an individual shedding CMV in their secretions (community acquired). Recipients with primary infection due to organ transplantation are more likely to experience CMV shortly after cessation of prophylaxis. When recognized early, these infections may have limited symptoms with viremia as the most common manifestation. Community-acquired CMV may occur at any time after transplant and because it often is unanticipated, may be more severe. Since the majority of adults are CMV seropositive at the time of transplant, this mode of acquisition is more common in pediatric settings.
Reactivation of latent-recipient CMV is less common with rates varying based on the choice of immunosuppression; induction with antilymphocyte therapies is associated with a higher incidence of CMV. There are multiple genotypes of CMV; gB 1 is most common. Superinfection typically occurs when both donor and recipient are CMV positive. Because CMV genotyping is not typically performed, the true incidence of CMV superinfection is not known. However, as CMV occurs more commonly in D+/R+ recipients than in D-/R+ recipients, it is likely that the donor strain is the causative agent of the majority of these infections.

**Pathogenesis/Risk Factors**

MHC-restricted, virus-specific, cytotoxic T lymphocytes play a major role in the control of CMV; consequently immunosuppressive agents that interfere with this host response increase the risk for CMV. Specifically, the use of antilymphocyte antibodies (a frequent component of induction therapy) that ablate lymphocyte function for prolonged periods and prompt the elaboration of proinflammatory cytokines is associated with CMV, as they both allow for reactivation of latent virus and enhance viral replication. Viral reactivation may be promoted by azathioprine, mycophenolate, and cyclophosphamide. Although calcineurin inhibitors (CNI) are not drivers of reactivation, they do allow for amplification of reactivated virus; tacrolimus is more potent than cyclosporine. The use of mTOR inhibitors may reduce the risk for reactivation. In addition to the net state of immunosuppression as defined by the choice of immunosuppression, risk factors for the development of CMV include CMV-seropositive donor, especially if the recipient is CMV seronegative, allograft rejection, coinfections with other viruses (HHV 6), host factors (including genetic factors), and severe hypogammaglobulinemia. Recently, assays designed to assess the cell-mediated immune (CMI) response have been used to assess the risk for CMV. One example of this is the QuantiFERON-CMV assay, which assesses cell-mediated immunity by measuring interferon (IFN)-gamma levels produced by CD8-positive T cells following in vitro stimulation with CMV antigens. Individuals with reduced responses to CMV stimulation were at greater risk for CMV; those who failed to respond to any stimulation were at the highest risk. Allograft rejection and CMV have a uniquely bidirectional interaction, whereby the proinflammatory environment created by rejection and the additional treatment with immunosuppressive agents prompt the reactivation and amplification of CMV and CMV upregulates antigens that promote alloreactivity leading to acute and chronic rejection syndromes.

**Diagnosis**

Prompt recognition of CMV is imperative to prevent complications and to improve outcomes. This requires initial consideration based on the clinical presentation and risk assessment. Recipients presenting with unexplained cytopenias, GI complaints, or both should be assessed for CMV, especially if they have risk factors and have recently suspended prophylaxis. Currently, assays targeted at detection of viremia are most commonly used for diagnosis. In particular, NAT uses polymerase chain reaction (PCR) technology to measure CMV DNA in plasma to rapidly and accurately determine the presence of CMV in the blood. This assay is quantifiable and higher values typically correlate with more severe disease. It also can be used to follow the course of treatment as effective treatment is accompanied by resolution of viremia. NAT has been notable for interlaboratory variability but the development of an international standard has reduced this variability; regardless comparison of values between different laboratories can still be confusing. Antigenemia testing (a semiquantitative fluorescent assay that stains circulating neutrophils for CMV early antigen [pp65]) can be used to assess viremia. Similar to NAT, this assay can be used to follow the response to treatment. Both assays may be negative in the presence of active infection, especially GI, neurological, and retinal CMV. Consequently, histopathological diagnosis remains the gold standard for CMV diagnosis and patients with consistent clinical syndromes and negative tests for viremia should undergo tissue biopsy. Because of the delay in diagnosis and lower sensitivity, neither culture nor serological testing is routinely used for CMV diagnosis.

**Prevention**

Because CMV has been associated with worse outcomes in kidney transplant recipients, risk-based prevention is essential. Universal prophylaxis and preemptive therapy have been used routinely. Universal prophylaxis involves administration of an antiviral during a risk period typically defined by the recipient and donor’s CMV serostatus. The preemptive approach uses quantitative assays to monitor for CMV reactivation/infection at specified time points posttransplant. Patients with evidence of CMV are then treated with antivirals. There are advantages and disadvantages to both strategies. Prophylaxis may reduce the indirect effects of allograft rejection and opportunistic infection and decrease the risk for infection with other herpesviruses; the cost and toxicity of prolonged antivirals may be impediments to this approach. The preemptive strategy may reduce the cost of medications and the medication-related adverse events and it also may allow for more effective recovery of the host immune response. But coordination of care and the cost of monitoring may affect the feasibility of this strategy. Notably, neither approach has prevented infection with resistant CMV strains.

Current guidelines recommend that patients at highest risk for CMV receive antiviral prophylaxis for 3 to 6 months after transplant, with many centers opting for 6 months prophylaxis based on a study comparing 3 to 6 months in a group of CMV D+/R− kidney recipients. Although there are studies supporting the use of acyclovir, valacyclovir, and ganciclovir, the majority of centers currently use valganciclovir for prophylaxis, given the ease of administration and improved outcomes. The optimal dose of valganciclovir for prophylaxis is not known. For CMV-seropositive recipients, some centers use 450 mg daily rather than the recommended dose of 900 mg, but at least one center has suggested that the lower dose may not be appropriate for
CMV D+/R– recipients.69,70 Regardless, valganciclovir dosing should be determined solely on the basis of kidney function and dose reductions should not be made because of medication-related toxicities, including cytopenias.62

Treatment
Treatment of CMV requires administration of an effective antiviral until all signs and symptoms have resolved; a minimum of 2 to 3 weeks is considered standard.62 The vast majority of CMV isolates are susceptible to ganciclovir and IV ganciclovir (dose 5 mg/kg every 12 hours, dose adjusted for kidney dysfunction) is the standard regimen.40,62 For mild to moderate disease, valganciclovir (dose 900 mg/kg twice daily, dose adjusted for kidney dysfunction) can be considered.71 Because CMV infection often is a consequence of “overimmunosuppression,” it is important to reassess the immunosuppressive regimen and consider if this can be reduced. Reduction in dose or suspension of mycophenolate or azathiorpine is most commonly considered. During treatment, weekly monitoring of CMV viral loads is recommended to determine response to treatment. At 2 weeks, a log decrease in viral load should be demonstrated. If the viral load does not decline by 2 weeks, the patient should undergo testing for CMV resistance using a genotypic assay.40,62 Risk factors for resistance include CMV D+/R– status and prolonged subtherapeutic exposure to ganciclovir or valganciclovir.62,72 Ganciclovir-resistant patients may be treated with foscarnet or cidovir; investigational agents also may be available.40,62 Both foscarnet and cidovir are nephrotoxic and close monitoring of kidney function and electrolytes during therapy is critical.

There are several concerns regarding treatment of CMV. In some cases (especially involving the GI tract), viral loads do not accurately reflect the extent of CMV disease.62 Endoscopic evaluation should be performed before suspension of treatment to ensure eradication of infection. In addition, recurrent disease can occur following completion of treatment. Although guidelines have suggested that there may be a role for either secondary prophylaxis or monitoring for relapse with viral load monitoring, there are no trials demonstrating that either approach is beneficial.62 If CMV occurs during usual risk periods, prophylaxis may be resumed after completion of therapy. Regardless of which approach is chosen, the risks and benefits of additional prophylaxis and monitoring should be balanced against observation and standard care.

Epstein-Barr Virus and Posttransplant Lymphoproliferative Disease
Similar to CMV, EBV is a member of the herpesvirus family. Acquired in childhood by person-to-person spread primarily via saliva, the vast majority of adult kidney recipients are seropositive before transplant. In the normal host, EBV first infects oropharyngeal epithelial cells then B lymphocytes, where it establishes latency. After kidney transplant, EBV can manifest in diverse ways.73 Most commonly, it reactivates asymptomatically, but infectious mononucleosis-like syndromes and PTLD also can occur. EBV viremia is common after kidney transplant, with one study showing that 40% of 383 kidney recipients monitored regularly experienced EBV viremia with median time to viremia of 31 days.74 Viremia is most common in EBV-seronegative recipients of seropositive donor kidneys and has been associated with allograft loss and an increased risk for opportunistic and bacterial infections.25

Posttransplant Lymphoproliferative Disease
The most significant complication of EBV infection is EBV-associated PTLD. Adult kidney transplant recipients are at lower risk for this compared with other organ transplants, with an estimated incidence of 1% to 2%.76 The major risk factors for PTLD include primary infection (EBV D+/R–) and the net state of immunsuppression.73,76 The choice of immunosuppressive agent used in induction has been an important factor in the subsequent development of PTLD; antithymocyte globulin and belatacept have both been implicated and EBV-seronegative status is a contraindication to the use of belatacept.77 PTLD is generally divided into early PTLD (occurring in the first year posttransplant)—which is more likely to be associated with primary EBV infection, polymorphic, and involve the allograft—and late PTLD (occurring after the first year), which is usually a disease of older recipients, EBV negative, and monoclonal.73

Diagnosis of Epstein-Barr Virus and Posttransplant Lymphoproliferative Disease
The clinical presentation of EBV and PTLD can be quite variable.73 A cause of fever of undetermined origin, it can also present with a mononucleosis-like syndrome. Cytopenias may occur and involvement of the allograft, GI tract, lungs, liver, and CNS have all been described; extranodal disease is especially common with late PTLD. Constitutional B symptoms are sometimes present. Quantitative NAT of whole blood, peripheral blood mononuclear cells (PBMCs), plasma, or serum is often used as the first step for the diagnosis of acute EBV and PTLD, but there are a number of issues that limit the utility of this assay for diagnostic purposes.73,76 It is important to recognize that specimen selection has a major effect on viral load measurements, since higher viral loads will be seen with whole blood cells or PBMCs. Furthermore, there is still some interlaboratory variability related to the absence of an international reference standard, making it difficult to compare results obtained from different laboratories. Finally, it is important to recognize that PTLD can occur in the absence of viremia and in the presence of viremia may occur in the absence of PTLD. Histopathological diagnosis is ultimately required to make the diagnosis. The World Health Organization has devised criteria for staging PTLD based on the clinical presentation, with early (stage I) disease defined as benign polyclonal proliferation, stage II polymorphic disease, stage III monomorphic B- or T-cell lymphoma/neoplasms, and stage IV disease defined as classical Hodgkin lymphoma.79
Treatment and Prognosis of Posttransplant Lymphoproliferative Disease

Because PTLD often is a reflection of a more immunosuppressed state, a key component of treatment is the reduction of immunosuppression, which may result in a significant reduction in disease burden for some individuals. However, this does increase the risk for rejection and many patients will require additional interventions, including rituximab, chemotherapy, surgery, and/or radiation oncology. Although PTLD is often EBV associated, there is no role for antivirals. A multidisciplinary approach, involving transplant physicians, oncologists, and infectious disease specialists is recommended to optimally manage these patients.

Prevention

Prevention of PTLD should include a multitiered approach. For seronegative recipients, belatacept should be avoided. Serial viral load monitoring can be used to titrate immunosuppression, especially during the first year post-transplant. Prevention of CMV may help decrease the risk as CMV has been identified as a potential cofactor for the development of PTLD. Rituximab has been used for some patients with persistently elevated EBV viral loads, but is associated with an increased risk for other infections and, in the absence of controlled trials, is not currently recommended. More recently, there has been interest in using T cell–based therapies directed specifically against EBV. Not universally available yet, this approach offers promise for future therapeutic intervention.

BK Virus

BK virus is a common posttransplant viral infection, affecting predominantly kidney transplant recipients, although case reports have implicated it as a cause of acute kidney injury in solid organ recipients. It was first identified in the urine of a kidney transplant recipient with ureteral stenosis in 1971. The virus is a member of the polyoma family, which includes JC virus, Saint Louis polyomavirus, and New Jersey polyomavirus. There are at least six different genotypes identified, and each has a different geographical predominance. Genotype I is the most common worldwide, and the primers utilized in PCR detection assays are based off this strain. Most adults are seropositive for BK, which after primary infection in childhood establishes latency in the uroepithelium. It reactivates in the setting of immunosuppression, leading to viremia, which if unchecked progresses to viremia and BK nephropathy. Approximately one-third of kidney transplant recipients develop BK viremia, about 20% develop viremia, and <10% develop BK nephropathy.

Risk Factors

Several common risk factors for BK viremia and nephropathy have been identified. The overall degree of immunosuppression is probably the most important factor, as the prevalence of BK infection has increased as more potent immunosuppression has been introduced and factors augmenting the cumulative immunosuppressive burden, such as rejection episodes or greater HLA mismatching also increase the risk. Older age, male sex, diabetes, and use of ureteral stents also have been implicated as BK risk factors. There is growing evidence to suggest that the infection is donor derived and the absence of prior recipient infection may increase the risk for nephropathy. In one study, donor, but not recipient BK antibody titers were predictive of BK viremia and nephropathy; recipients of high antibody titer donor kidneys had a 10-fold increased risk for BK viremia (10.1; 95% CI, 3.5 to 29; P < 0.001), corroborating earlier work by Bohl et al.

Viral Load Monitoring, Diagnosis, and Prevention of BK Nephropathy

BK antibodies are not protective and no effective antiviral prophylaxis has yet been identified. Most centers screen prospectively for BK infection by measuring BK viral loads in plasma or urine. Since the majority of BK infections are detected in the first year after transplant, screening is concentrated in the early posttransplant period, although late BK infections have been reported and BK infection should be included in any investigation of allograft dysfunction. The American Society of Transplantation (AST) consensus guidelines recommend screening patients for BK viremia every 1 to 3 months for the first 2 years posttransplant. The majority of transplant centers screen using serum BK PCR but this approach is not mandated and urine BK PCR remains a popular alternative. Due to the lack of a universal standard assay for real-time BK PCR, there is significant interlaboratory variability in the assay’s quantification; therefore consistency in the laboratory used for viral load monitoring is important and results that are inconsistent with a patient’s clinical course should be questioned. Although a BK viral load >4 log copies/mL is “presumed” BK nephropathy, this diagnosis can only be made by kidney biopsy. Although biopsy may not change management, it does provide useful information regarding the degree of inflammation and fibrosis, and by extension, the risk for allograft loss. BK nephropathy on biopsy can be mistaken for acute cellular rejection with a lymphocytic infiltrate and tubulitis, and definitive diagnosis is made by demonstrating the presence of immunohistochemical stains directed at the SV-40 large T antigen or VP-1 capsid protein (PAB-597 stain).

Treatment

The cornerstone of BK viremia and nephropathy treatment is the careful reduction of immunosuppression. A variety of approaches have been employed to achieve this, including discontinuation of the antimetabolite, dose reduction of the CNI, switching CNIs or replacing them with another agent altogether. In vitro data suggest that sirolimus and cyclosporine may have inhibitory effects on BK viral replication, whereas tacrolimus is permissive, suggesting that reduction of tacrolimus may be most beneficial in eradicating BK infection. Both short- and longer-term data suggest that immunosuppression reduction results in BK viral clearance in the majority of patients and does not have a negative effect on allograft or patient survival. At our center, we discontinue the antimetabolite and monitor BK viral loads every...
2 to 4 weeks thereafter; if the viral load does not respond, we then decrease the CNI, aiming for a 25% reduction in the trough level. Anecdotally, we have had success in clearing BK infection in patients with persistent viremia despite tacrolimus trough levels in the 4 to 5 ng/mL range by switching them to cyclosporine and aiming for a trough level of 50 to 75 mg/dL. Serum creatinine must be monitored closely during this period of reduced immunosuppression.

Although retrospective data had suggested a role for fluoroquinolone antibiotics in the prevention of BK infection, a prospective, double-blind, randomized trial of levofloxacin prophylaxis to prevent BK infection in kidney transplant recipients failed to find any such benefit.\textsuperscript{108,109} After 3 months of treatment in the 154 patients enrolled in the study, there was no difference in the incidence of BK viruria (29% vs. 33.3%; \( P = 0.58 \)) but there were significantly more quinolone-resistant bacterial infections and tendonitis in the levofloxacin group.

There have been case reports suggesting success in treating BK with leflunomide, cidofovir, levofloxacin, and IV immunoglobulin, often in conjunction with immunosuppression reduction, but no large-scale, prospective trials to advocate for the use of any of these agents.\textsuperscript{91,110-112} There are also several reports of lower rates of BK viremia in patients maintained on sirolimus and increased viral clearance with conversion to mTOR inhibitors; however, given the increased risk for death demonstrated with sirolimus use in the kidney transplant population, we do not advocate for this as a first-line treatment approach.\textsuperscript{113-116}

**Hepatitis C**

Recent data from the National Health and Nutrition Examination Survey (NHANES) indicates that the prevalence of HCV infection in the general US population is low (~1%), but the ESRD population is enriched for HCV with a prevalence that ranges from 2.6% to 22.9% depending on the series.\textsuperscript{117,118} The DOPPS (Dialysis Outcomes Practice Patterns Study) identified length of time on maintenance dialysis as one of the most important predictors of HCV infection, with HCV seroprevalence of greater than 50% in those with more than 20 years of ESRD; blood transfusions, prior transplantation, and IV drug use were other risks for HCV acquisition.\textsuperscript{119} HCV transmission in dialysis units has been well described, emphasizing the importance of universal precautions without a need for patient isolation; in recognition of these risks, maintenance hemodialysis patients are categorized as PHS IRDs.\textsuperscript{13}

It is recommended by the Kidney Disease Initiative to Improve Global Outcomes (KDIGO) guidelines to screen all kidney transplant candidates for HCV infection.\textsuperscript{120} NAT for HCV RNA in the blood is preferred over antibody screening in high-prevalence areas, patients with unexplained elevations in hepatic transaminases, or in immunosuppressed populations who may be viral load-positive but never mount an antibody response (antibody-negative but NAT-positive); additionally NAT enables identification of patients who have spontaneously cleared the infection (antibody-positive but NAT-negative) and those with early infection. All patients who are HCV NAT-positive should be referred to a hepatologist for an assessment of liver disease severity before transplantation.

**Kidney Transplantation in Hepatitis C Virus-positive Patients**

Kidney transplantation offers a survival benefit for HCV-positive patients over remaining on maintenance dialysis; in contemporary case series, cardiovascular disease, rather than cirrhosis, was the predominant cause of death on the waitlist.\textsuperscript{121} Although early case series suggested that post-transplant patient and allograft outcomes for HCV-positive patients were similar to HCV-negative recipients, more contemporary data and metanalyses have indicated that outcomes are in fact worse.\textsuperscript{122} Older studies had identified cirrhosis as the main cause of death for HCV-positive transplant recipients, but newer data suggests that cardiovascular disease and diabetes are significant contributors to mortality.\textsuperscript{123} Allograft survival is also negatively affected by recipient HCV-positive status with a metanalysis reporting a hazard ratio (HR) of 1.7 (95% CI, 1.46 to 2.11) for graft loss, but not all studies have consistently shown a negative effect of HCV infection on kidney allograft survival.\textsuperscript{122}

There has been concern that the immunosuppression required for kidney transplantation could accelerate liver disease in HCV-positive recipients; HCV viral loads have been shown to increase after transplantation and historically cirrhosis was a main cause of patient mortality. However, in the limited case series that have had both pre- and posttransplant liver biopsies available, this was not the case. In a series report of 31 patients by Roth et al., 77% (24) had stable or improved histology on follow-up biopsy and only 23% had interval worsening of their liver fibrosis.\textsuperscript{124} Another series from France, with sequential posttransplant biopsies in 36 patients, showed a similarly benign posttransplant course; despite increased viral loads, >60% of patients in the study had stable liver fibrosis on repeat biopsy and only 3 patients developed cirrhosis by 20 years of follow-up.\textsuperscript{125}

Infections may be one source of the increased mortality observed in HCV-positive transplant recipients. Although some reports identified sepsis as an important cause of death in their HCV-positive patients, a recent prospective study from Spain did not observe a difference in the overall incidence of infection among HCV-positive and HCV-negative patients.\textsuperscript{126,127} However, they did observe a significant increase in bacteremia in HCV-positive recipients (HR, 3.14; 95% CI, 1.46 to 6.78; \( P = 0.002 \)).

**Use of Hepatitis C Virus-positive Donors**

Long waits for transplantation in the United States and the overall shortage of suitable donor kidneys have led many centers to explore means of expanding the donor pool by using “nonstandard” donors, such as those with HCV infection. The growing opioid abuse epidemic has increased HCV infection rates in certain regions of the United States, leading to an increase in both overdose deaths and donors with HCV infection. Historically, the use of HCV-positive organs
has been restricted to recipients with genotype 1 infection. Because donor HCV genotyping is not available before transplantation, clinicians assume HCV-positive deceased donors have genotype 1 infection, since this is the most prevalent genotype in the United States. However, superinfection with other HCV genotypes is possible. Since pan-genotypic, IFN-free, direct-acting antiviral (DAA) agents to cure HCV exist, this limitation to genotype 1 recipients may be outdated.

One of largest published single series describing the use of HCV-positive donors comes from Spain. Morales and colleagues reported the outcomes for 162 HCV-positive recipients of HCV-positive kidneys compared with 306 HCV-positive recipients of HCV-negative donors.128 Patient survival at 5 years was similar (84.8% in D+/R+ vs. 86.6% in D−/R+; \( P = 0.25 \)) but allograft survival was diminished (5-year allograft survival 58.9% in D+/R+ compared with D−/R+ 65.5%; \( P = 0.006 \)). A recent propensity score matched analysis performed using United Network for Organ Sharing (UNOS) data to address this question found that transplantation with a HCV-positive donor was associated with an increased risk for death (HR, 1.43; 95% CI, 1.18 to 1.76; \( P < 0.001 \)) and graft loss (HR, 1.39; 95% CI, 1.16 to 1.67; \( P < 0.001 \)) among HCV-positive recipients, an effect that was not explained by differences in acute rejection (OR, 1.16; 95% CI, 0.84 to 1.61; \( P = 0.35 \)).129 Given the time frame of the study, it is unknown if DAA eradication of HCV would have changed the outcome. The use of HCV-positive donors for HCV-positive individuals is associated with shorter wait times to transplantation (∼1 year less on average) but recipients should be counseled about the risks and benefits associated with the use of these donors.130 Whether HCV-positive donors may be safely used for HCV-negative recipients is currently an area of study now that the potential treatment options for HCV have expanded.131 Presumably, donors who are not viremic are much less likely to transmit HCV via transplantation; consequently there has been increasing interest in using these donors. More data are needed to determine the safety of HCV-positive donors.

**Treatment of Hepatitis C Virus With Direct-Acting Antiviral**

The initial KDIGO guidelines, during the era before DAA therapy, recommended treatment of HCV in all kidney transplant candidates.120 Until recently, this meant pretransplant treatment with IFN-based regimens, which have modest response rates to therapy and poor tolerability; treatment with IFN after kidney transplant has been associated with unacceptably high rates of acute rejection and graft loss. Since 2013 there has been a rapid expansion in the number of IFN-free DAA regimens approved to treat HCV infection. These regimens have been associated with HCV cure rates in excess of 95% in the general population and have demonstrated efficacy in kidney transplant recipients as well.132

DAA regimen selection for kidney transplant recipients is complex. Currently, the greatest number of therapeutic options exist for patients with genotype 1 infection, but this area is rapidly changing (the American Association for the Study of Liver Diseases [AASLD]/Infectious Diseases Society of America [IDSA] guidelines provide the most current treatment recommendations and are continuously updated as new information becomes available).133 Kidney function and DAA-immunosuppression drug–drug interactions must be taken into account when a DAA regimen is being selected. Sofosbuvir-containing regimens are not approved for use in patients with a glomerular filtration rate less than 30 mL/min. Regimens that contain simeprevir can increase cyclosporine levels and elbasvir/ grazaprevir, when coadministered with cyclosporine increases grazaprevir levels. In addition, regimens that require ritonavir boosting (such as dasabuvir/ombitasvir/ paritaprevir) will result in major increases in CNI blood levels and require significant CNI dose adjustment; these regimens are generally avoided in the posttransplant setting. CNI levels have been shown to fluctuate even after DAA treatment is completed, highlighting the need for careful monitoring of kidney function and drug levels both during and after therapy. Prescribers also need to be aware of issues of viral resistance, with appropriate testing for NS5a resistance mutations of genotype 1a patients depending on the regimen selected, as well as reports of hepatitis B reactivation while on HCV therapy. Treatment of HCV in kidney transplant recipients should be managed carefully with combined efforts by hepatologists, infectious disease specialists, and transplant nephrologists.

**Hepatitis B**

Unlike HCV, the prevalence of HBV in the US ESRD population is low (estimated to be around 1%), and likely due to efforts to vaccinate all chronic kidney disease (CKD) patients before their start of dialysis, improved infection control in dialysis units, and more widespread use of erythropoietin-stimulating agents rather than transfusions to manage anemia.134 All kidney transplant candidates should be screened for HBV infection at the time of transplant evaluation with measurement of hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), and core antibody (HBeAb), in addition to the regular screening conducted in dialysis units. Patients who are HBsAg-positive or have detectable HBV DNA should be referred to hepatology for evaluation and treatment. Patients who are HBeAg-positive have immunity, whether from vaccination or cleared infection (the latter if the presence of HBeAb is detected). Patients who are not immune should be vaccinated, preferably before the initiation of renal replacement therapy.

The initial outcomes for kidney transplantation in hepatitis B-infected recipients were poor. Ten-year patient survival was 55% and 10-year allograft survival was 36%.135 Cirrhosis was a frequent complication, developing in 28% by 5 years of posttransplant follow-up and hepatocellular carcinoma was common.136 However, the introduction of effective HBV therapies into routine clinical practice improved outcomes significantly. In a study of 1346 HBsAg-positive recipients transplanted from 2001 to 2007, 5-year patient survival was 85.3% and allograft survival was 74.9%, which was not significantly different from contemporary HBV-negative controls.137 A fivefold increased risk for hepatic decompensation among the HBV-positive recipients was observed; however, this complication only occurred in 1.3% of patients overall.
Before transplant, candidates with chronic HBV infection should be screened for cirrhosis as well as coinfection with HCV and hepatitis A and counseled to avoid other hepatotoxins (including alcohol). Because there is currently no cure for HBV infection, patients who are HBsAg-positive and/or DNA-positive should receive lifelong antiviral therapy and routinely screened for complications of chronic infection, including cirrhosis and hepatocellular carcinoma. Individuals who are HBCAb-positive may be at risk for reactivation of HBV after intense periods of immunosuppression, especially when B-cell depleting agents, such as rituximab, are used. In anticipation of rituximab treatment, all patients should be checked for hepatitis B and prophylactic antivirals considered for HBCAb- and/or HBsAg-positive individuals.

**Treatment of Hepatitis B Virus**

The improved outcomes for patients are due to a multitude of antiviral agents now available to treat HBV. Lamivudine is among the most widely used, but is not recommended for long-term prophylaxis due to its low barrier to resistance. Tenofovir disufamate is both highly potent and has a high barrier to resistance, but nephrotoxicity and its association with bone loss makes it an unattractive choice for chronic use in kidney transplant patients. Tenofovir alafenamide is a newer formulation that is effective against HBV and has a lower risk for associated kidney impairment and osteopenia. Entecavir is also highly effective and has a high barrier to resistance without nephrotoxicity, and is therefore often used for kidney transplant recipients who will require chronic HBV therapy.

**Use of Hepatitis B Virus-positive Donors**

HBV-positive kidneys have been explored as a means to increase the available donor pool and guidelines for their use have been developed by a work group from the American Society of Transplantation. The risk for transmission of HBV depends on several factors including the particular organ being transplanted, recipient HBV immunity, and the HBV prophylaxis strategy employed. HBsAg-positive donors are used least frequently and represent <1% of all deceased donors. They can be used in HBsAg-positive recipients, who will require lifelong treatment with entecavir or tenofovir regardless due to recipient HBV status; additionally, hepatitis B immunoglobulin (HBIG) administration could be considered if HBsAb titers are low. HBsAg-positive kidneys have been used in HBsAb-positive recipients with and without antiviral prophylaxis with minimal transmission risks. The use of HBsAg-positive donors in HBV-naive or unvaccinated patients is not advised. HBcAb-positive donors can be used in HBcAb-positive and/or HBsAg-positive recipients and no prophylaxis is required. Hepatitis B-naive or unvaccinated recipients can also receive HBcAb-positive kidneys since the risk for transmission is low but guidelines suggest lamivudine may be considered for 1 year posttransplant as prophylaxis. All recipients receiving kidneys from HBV-positive donors should have posttransplant monitoring with HBV DNA viral loads, surface antigen, and core antibody (for individuals without prior infection), regardless of their immune status.

**Human Immunodeficiency Virus**

HIV infection is a known risk factor for the development of CKD and ESRD. Widespread adoption of potent antiretroviral therapy (ART) has contributed to a decline in ESRD among whites with HIV infection, but rates of ESRD are still disproportionately higher among affected blacks. Kidney transplantation is accepted as the ideal therapy for ESRD, even among HIV-positive individuals, but HIV-positive patients have diminished access to the waiting list and are less likely to achieve kidney transplantation. Of the 309 HIV-positive patients evaluated at a single transplant center from 2000 to 2007, only 20% achieved wait-listing compared with 73% of HIV-negative patients during the same time period. A study of waitlist outcomes for HIV-positive patients demonstrated that although waitlist mortality was similar to HIV-negative patients (adjusted hazard ratio [aHR], 1.03; 95% CI, 0.89 to 1.20; P = 0.67), HIV-positive candidates were less likely to receive a deceased donor transplant (aHR, 0.87; 95% CI, 0.74 to 1.01; P = 0.07) and significantly less likely to achieve living donor transplantation (aHR, 0.53; 95% CI, 0.44 to 0.64; P <0.001). However, kidney transplantation is associated with a survival benefit, compared with remaining on the waitlist (adjusted risk ratio [aRR], 0.21; 95% CI, 0.10 to 0.42; P <0.001), for HIV-positive patients, as has been observed for other high-risk patient groups.

Due to high patient mortality and high rates of allograft failure in HIV-positive patients transplanted in the pre-ART era, HIV was once considered a relative contraindication to transplantation. However, with improved HIV patient survival after the widespread implementation of potent ART therapy, this relative contraindication was reconsidered. After numerous case series reporting promising results, the National Institutes of Health (NIH) funded a multicenter prospective trial to assess feasibility of kidney transplantation in HIV-positive patients; this study enrolled 150 patients at 19 centers across the United States and followed them for 3 years. Patient survival was 88% and allograft survival was 73.7% at 3 years, similar to outcomes for older kidney recipients as reported in the Scientific Registry of Transplant Recipients (SRTR), but outcomes were worse for HCV-coinfected recipients. Since the publication of the results of the NIH trial, several groups have examined the national experience with HIV-positive transplantation, using registry data. One study compared outcomes for 492 recipients with HIV and 147 recipients with HIV/HCV coinfection to an uninfected reference group. HIV monoinfected patient mortality (HR, 0.90; 95% CI, 0.66 to 1.24) and allograft loss (HR, 0.60; 95% CI, 0.40 to 0.88) were not statistically different, but there was an increased risk for death (HR, 2.26; 95%, 1.45 to 3.52) and graft loss (HR, 2.59; 95% CI, 1.60 to 4.19) in the HIV/HCV coinfected patients. A “mate kidney” analysis, to control for donor quality, found similar results, as did a study matching HIV-positive recipients with HIV-negative controls. Interestingly, Locke et al. demonstrated that experience in HIV-positive transplantation, as reflected in a center’s participation in the NIH multicenter trial, did not affect outcomes (patient survival aHR, 1.13; P = 0.63 and...
allograft survival aHR, 1.08; P = 0.71), but there was an era effect, with patients transplanted between 2008 and 2011 having better outcomes than those transplanted earlier.149

**Acute Rejection**

Despite the fact that HIV infection is a state of overall immunosuppression, higher than expected rates of acute rejection have been consistently observed. In the NIH multicenter trial, the incidence of rejection was 31% in the first year, compared with the expected Scientific Registry of Transplant Recipients (SRTR) 1-year rejection rate of 12.3% in HIV-negative kidney transplant recipients.145 A similarly high incidence of rejection has been reported in multiple subsequent case series from the United States and Europe.150,151

Excess acute rejection risk may not be entirely due to immune dysregulation from HIV infection; drug–drug interactions, selection of induction and maintenance immunosuppression as well as viral suppression likely also play a role. A recent study demonstrated that patients who had undetectable viral loads for less than 2 years before transplant were 2.48-fold more likely to experience acute rejection after kidney transplantation.152 An analysis of the SRTR database revealed that HIV-positive patients are less likely to receive lymphocyte-depleting induction therapy than HIV-negative controls (31.4% vs. 55.9%), but use of antithymocyte globulin was associated with a lower risk for rejection (RR, 0.39; 95% CI, 0.18 to 0.87; P = 0.02). Maintenance immunosuppression is also important. In that same study, patients on maintenance sirolimus had a higher risk for rejection (aRR 2.15; 95% CI, 1.20 to 3.87) than those on a CNI.153 Data from a single-center case series suggested that tacrolimus use in HIV-positive recipients is associated with a lower acute rejection risk (21%) than cyclosporine (58%; P = 0.003).154

**Drug–Drug Interactions**

Drug–drug interactions between ARVs and CNIs are complex. Protease inhibitors (PIs), historically a main component of ARV regimens, are potent inhibitors of the cytochrome P450 (CYP)3A enzyme system, which is the main metabolic pathway for CNIs. When PIs and CNIs are coadministered, the result is higher CNI levels, necessitating CNI dose reductions. For patients on a PI and cyclosporine this means a four- to fivefold lower cyclosporine dose with a 50% increase in the dosing interval, whereas patients on tacrolimus and a PI require an 80% dose decrease and a sevenfold increase in the dosing interval.155

Non-nucleoside reverse transcriptase inhibitors (NNRTI) generally induce CYP3A enzyme activity and cause subtherapeutic levels, but individual effects can vary by NNRTI; this can be more easily overcome by increasing the CNI dose to achieve the desired trough level. In light of these complex interactions, many transplant professionals prefer the use of PI-free regimens whenever possible, favoring regimens based on integrase inhibitors, which permit more "traditional" CNI dosing and have been shown to be both safe and effective in the transplant setting.156 Alternatively, one could consider using belatacept in EBV seropositive recipients to avoid CNI–PI interactions, which has been described in several case reports.157

**Infection**

Infection is a common complication of HIV-negative transplantation and of special concern in the HIV-positive recipient. In the NIH trial, 38% of patients had an infectious complication requiring hospitalization, with the majority of these infections being bacterial in nature. The most common sites involved were the genitourinary tract (26%), the respiratory tract (20%), and the bloodstream (19%).145 The authors noted that infections of any type were twice as common among recipients who received antithymocyte globulin induction. Of 150 recipients, 5 developed BK nephropathy, similar to the prevalence observed in the HIV-negative transplant population. A more contemporary study using SRTR data linked to Medicare claims failed to find an increased risk for infection associated with induction immunosuppression in HIV-positive kidney transplant recipients; rates of infections overall in the first year were similar among HIV-positive patients who received no induction, antithymocyte globulin or anti-interleukin-2 receptor antibodies.158 The most common infection in this national cohort was of the urinary tract. Importantly, patients who received induction of either type spent fewer days in the hospital, had fewer readmissions overall, and had superior death-censored graft survival than those who did not receive induction immunosuppression.

Opportunistic infection prophylaxis for HIV-positive recipients is similar to the approaches used in HIV-negative patients; no HIV-specific data exists to suggest the need for more aggressive prophylaxis. The American Society of Transplantation Infectious Diseases guidelines outline one approach.159 The authors suggest lifelong prophylaxis against *Pneumocystis* pneumonia, ideally with trimethoprim-sulfamethoxazole but atovaquone or dapsone can be substituted for patients with sulfa allergies. CMV prophylaxis is also recommended for at-risk recipients and either valganciclovir or ganciclovir can be used; at many centers the dosing (450 vs. 900 mg/d) and duration of therapy (3 vs. 6 months) mirrors that which is used in the HIV-negative population. Although fluconazole was used selectively by some centers in the NIH trial as antifungal prophylaxis, many centers prefer nystatin to avoid drug–drug interactions with CNIs. Prophylaxis for infections such as toxoplasmosis (when CD4 ≤200 cells/mm³) with trimethoprim-sulfamethoxazole and *Mycobacterium avium* complex (when CD4 ≤75 cells/mm³) with azithromycin is also recommended, but since most HIV-positive transplant recipients have robust CD4 counts pretransplantation and rarely have prolonged periods of severe lymphocytopenia posttransplant, this is rarely required. Nine months of isoniazid therapy for any patient with previously untreated latent *Mycobacterium* TB is strongly advised.

**Use of Human Immunodeficiency Virus-positive Donors**

Whether HIV-positive individuals will be a safe and significant contributor to the donor pool is unknown. The most extensive experience using HIV-positive donors comes from South Africa. Muller et al. reported the results of 27 patients transplanted with kidneys from HIV-positive deceased donors, all with lymphocyte-depleting induction and...
tacrolimus-based immunosuppression. Acceptable outcomes were reported, with patient and allograft survival both 84% at 3 years. Although these results provide evidence of feasibility for HIV-positive to HIV-positive transplantation, the HIV-positive population in the United States is quite different.

In the United States the National Organ Transplantation Act, passed in 1984 specifically prohibited organ donation by HIV-positive individuals and the signage of the HIV Organ Policy Equity (HOPE) Act in November 2013 was a significant departure from this policy. The HOPE Act authorizes research in the area of HIV-positive to HIV-positive organ donation and specific research criteria for studies employing these organs have been established, with provisions for both living and deceased donors. To date, no living HIV-positive individual has served as a kidney donor but several deceased HIV-positive donor kidney transplants have been performed both in the United States and in Europe.

Using data from the Nationwide Inpatient Sample, the HIV Research Network, and UNOS, it was estimated that there were 500 potential HIV-positive donors in the United States per year; but these sources lacked necessary information to assess donor organ quality. A study of HIV-positive patients who died “in HIV care” in Philadelphia with more granular clinical information was only able to identify 13 potentially suitable HIV-positive donors over 5 years. The median kidney donor profile index (KDPI), a measure of organ quality, was 95%, indicating that these organs would be considered marginal kidneys. Use of HIV-positive donors in the United States has the potential to increase access to transplantation for HIV-positive individuals, but the extent to which these organs will contribute to the donor pool remains unknown and organ quality may be of concern. A multicenter trial using HIV-positive donors is underway and should provide useful information to guide future use of HIV-positive donors.

**Fungal Pathogens**

Kidney transplant patients are at increased risk for opportunistic infections due to diverse fungal pathogens, including Candida species, Aspergillus, Cryptococcus, and Pneumocystis. A US national survey of fungal infections revealed Candida infections to be most common (accounting for 49% of all infections); Cryptococcus occurred in 15% and Aspergillus in 14% of surveyed patients. Endemic mycoses were seen in 10% and Pneumocystis was relatively uncommon, accounting for 1% of infections in kidney recipients. Risk factors and clinical presentation vary based on the pathogen and the prophylactic strategy.

**Candida**

In the Transnet multicenter survey, Candida albicans was the most common Candida species found after transplantation and bloodstream infections were the most common site of infection. Because of the methodology used to collect cases in Transnet, mucocutaneous infections, the most common manifestation of Candida, were not captured. Candida also has been associated with intraabdominal infections (more commonly in kidney pancreas recipients), UTIs, and device-related infections. Candiduria poses a unique situation in the kidney transplant recipient. Because this may simply represent colonization, especially in women, it is important to differentiate infection from colonization. Guidelines recommend against treatment of asymptomatic candiduria. It is important to recognize symptomatic infection and fungus balls that can result in obstructive uropathy especially in recipients with poor bladder function or will be undergoing urinary tract manipulation; treatment is indicated in these circumstances.

Risk factors for Candida infections are similar to those found in the general population and include diabetes mellitus, renal replacement therapy, broad-spectrum antibiotic use, parenteral nutrition, central venous catheters, and neutropenia. Kidney pancreas transplant recipients who undergo enteric drainage are at increased risk for Candida infections due to the surgical procedure. Overall mortality in transplant recipients with Candida infections in the Transnet survey was 25% with mortality highest in patients infected with non-albicans Candida species. Additional risk factors for mortality in kidney recipients included the presence or hepatic and/or renal insufficiency, congestive heart failure, and the use of amphotericin B.

Optimal treatment of Candida infections depends on the site and species. It is important to remove any implicated devices (e.g., IV catheters) whenever possible. Fungus balls may require surgical removal. The choice of antifungal should be determined based on the species. Empiric treatment with echinocandins can be considered until the species is identified; however, these agents do not penetrate well into the urinary tract and consequently should be avoided for UTIs. AAOles are preferred for the treatment of UTIs. The vast majority of C. albicans species are susceptible to fluconazole; treatment of the less-susceptible non-albicans species may require treatment with echinocandins, voriconazole, or amphotericin B (lipid formulation). If azoles are used, it is important to consider the potential for drug interactions with CNI and with mTOR inhibitors and dose adjustments of the immunosuppressive agents are often required at the time of initiation of azole therapy.

**Cryptococcus**

The multicenter epidemiological study of fungal infections in transplant patients (Transnet) identified Cryptococcus as the second most common invasive fungal infection in kidney transplant recipients. This opportunistic infection typically occurs late after transplant with a median time of onset of 575 days posttransplant. The most common manifestations are CNS disease (basilar meningitis) and pneumonia. Risk factors for the disease include end-stage liver disease and lymphocyte depletion secondary to alemtuzumab or antithymocyte globulin. Given the late onset of infection, environmental exposure may also play a role. Mortality associated with this infection is high; Transnet revealed a 12-month
mortality of 27% although other studies estimated mortality of approximately 14% with baseline kidney failure a risk factor for mortality.\textsuperscript{26,168}

Prompt recognition and treatment of cryptococcal infection is critical to patient survival. Many patients present with typical signs and symptoms of basilar meningitis, including headache and visual symptoms, including diplopia. Pulmonary nodules, skin nodules, liver, renal, and rarely bone and joint disease have also been described.\textsuperscript{167} Because of the predilection of Cryptococcus for CNS involvement, patients with extraneural disease should undergo lumbar puncture to exclude meningeal involvement. Lumbar punctures should include measurement of opening pressure (an important prognostic indicator) as well as glucose, protein, cell count, fungal culture, and cryptococcal antigen. A serum cryptococcal antigen can be performed but a negative serum antigen does not exclude the possibility of Cryptococcal disease and lumbar puncture and/or tissue biopsy may still be warranted in patients suspected of infection.\textsuperscript{167}

Optimal treatment of infection depends on the site of disease but ideally includes a 2-week induction phase with a lipid-based amphotericin and 5-flucytosine, followed by fluconazole, for patients with CNS or more severe disease.\textsuperscript{167} The optimal duration of therapy is unknown and it is important to follow patients with repeat lumbar punctures and imaging as appropriate to ensure disease resolution. An important complication of cryptococcal infection has been the development of immune reconstitution inflammatory syndrome (IRIS), especially associated with rapid tapering of immune suppression.\textsuperscript{169} This has been manifested by worsening of cryptococcal symptoms and findings; serial lumbar punctures have been required in the presence of IRIS and meningitis to decrease the intracranial pressure. There is no specific treatment for this complication but corticosteroids have been beneficial in anecdotal reports.\textsuperscript{167}

**Aspergillus**

Aspergillus was noted to cause 14% of invasive fungal infections in kidney recipients in the Transnet study.\textsuperscript{26} Typically seen in the first 6 to 9 months posttransplant, mortality is high; Transnet reported a 12-month mortality of 41% for invasive aspergillosis, a rate similar to that seen in a large multicenter multinational study.\textsuperscript{26,170} Notably, graft loss was also high, affecting 20% of patients with invasive aspergillosis.\textsuperscript{170} The majority of infections involve the lungs, although extrapulmonary and disseminated infection can occur. Risk factors for the development of invasive pulmonary aspergillosis in the multinational study include pretransplant chronic obstructive pulmonary disease, serious posttransplant infections, and impaired allograft function.\textsuperscript{171} Additional risk factors include hemodialysis and intensified immunosuppression, including prolonged high doses of corticosteroids.\textsuperscript{172} Diagnosis requires differentiation of colonization from infection; consequently pulmonary infection requires a combination of imaging (typically computed tomography) and respiratory tract microbiological sampling. Extrapulmonary sites often require tissue biopsy for pathology and culture. Galactomannan obtained from serum or bronchoalveolar lavage can be a useful adjunct to diagnosis but a negative serum galactomannan does not exclude the diagnosis.\textsuperscript{172} The treatment of choice has been voriconazole, although there are significant drug interactions that must be managed, especially with CNIs and mTOR inhibitors.\textsuperscript{172} In addition, the IV formulation of voriconazole includes a cyclodextran base that can cause hyperviscosity when administered to individuals with CKD. Other azoles, including posaconazole and isavuconazole, echinocandins, and lipid formulation of amphotericin also are effective. It is unknown whether combination therapy will improve outcomes, but the multinational study did not show any benefit in their cohort of renal transplant recipients.\textsuperscript{170}

**Pneumocystis jirovecii**

*Pneumocystis jirovecii* (formerly known as *Pneumocystis carinii*) is an uncommon cause of pneumonia in kidney transplant recipients, accounting for 1% of fungal infections in the Transnet study.\textsuperscript{26} This low incidence likely reflects the common use of trimethoprim sulfamethoxazole in the early posttransplant period. Although relatively uncommon, mortality can be quite high. Increased immunosuppression, especially with agents that reduce the absolute CD4 count, high doses of corticosteroids, CMV, rejection, and proximity to other patients with *P. jirovecii pneumonia* (PJP) are all recognized risk factors for PJP.\textsuperscript{173} Radiographic findings are variable and diagnosis of PJP requires sampling of respiratory secretions, typically via bronchoscopy; cytology and PCR often will provide the diagnosis. Because the burden of organisms is lower than seen with patients with HIV infection, biopsy may be required to exclude the diagnosis.\textsuperscript{173} Serum beta-D-glucan is often very elevated and this may be a clue to the diagnosis. The treatment of choice is high-dose trimethoprim sulfamethoxazole coupled with a tapering course of higher-dose corticosteroids.\textsuperscript{173} Given the potentially poor outcomes in patients with PJP, it is important to provide prophylaxis to at-risk individuals. Commonly 6 to 12 months of trimethoprim sulfamethoxazole is recommended after transplant but longer courses should be considered for patients requiring higher doses of immunosuppression, including for the treatment of rejection. Individuals with CMV are also at increased risk for PJP, so some centers reintroduce PJP prophylaxis for patients who develop CMV infection. Alternative regimens, including atovaquone and dapsone (for patients with normal G6PD levels), can be considered for patients who are allergic to trimethoprim sulfamethoxazole.\textsuperscript{173}

**BACTERIAL INFECTIONS**

Bacterial infections are a major cause of morbidity and mortality after transplant. Surgical site infections, pneumonias, and diabetic foot infections are all seen, but the most common infections are those related to the urinary tract. The involved site may be anticipated based on the timing after transplant with surgical site infections occurring in the first month and pneumonias occurring related to hospital acquisition early and to more typical bacterial pathogens (e.g., *Streptococcus pneumonia* and *Legionella* species) in the later period. Kidney
transplant recipients are at increased risk for reactivation of TB and opportunistic bacterial infections, including with Nocardia species. It is important to consider the diversity of pathogens when evaluating patients presenting with signs and symptoms of infection. The net state of immunosuppression, latent infections, and new environmental exposures all should be considered when developing a diagnostic plan. In many cases, more invasive testing may be required to confirm a diagnosis.

Urinary Tract Infections

UTIs are the most common bacterial infection seen in kidney transplant recipients with a prevalence of 23% to 75%. Although most commonly seen in the early posttransplant period, it is important to realize that UTIs can occur at any time following transplant, especially in women. Pyelonephritis and bloodstream infections are commonly seen; in one survey of bloodstream infections after kidney transplant, 75% were attributed to UTIs. Whether UTIs have a significant effect on long-term allograft function is controversial. The varying definitions for UTI, variable findings based on timing of infection posttransplant, and lack of uniform measures to assess kidney function used in clinical studies make it difficult to assess the overall effect. Regardless, these infections have been associated with increased mortality and at least acute impairment of kidney function and possibly long-term allograft damage. Risk factors for UTI vary with timing after transplant and include female sex, diabetes mellitus, ureteral stents, urinary tract catheterization, urinary tract abnormalities (including reflux), immunosuppression (antithymocyte globulin, mycophenolate), reduced allograft function, en bloc double kidney transplants, deceased donors, and acute rejection.

It may be difficult to recognize UTI in kidney transplant recipients because the usual symptoms may not be present given the disruption of the usual neural pathways. Allograft tenderness is often seen. Standard definitions of UTI reflect those used in nontransplant recipients and include the demonstration of both pyuria and bacteriuria. E. coli remains the most common organism causing UTIs. It is important to perform susceptibility testing for urinary tract isolates since there have been increasingly frequent reports of multidrug-resistant pathogens. Ultrasound and computed tomography imaging may confirm the diagnosis of pyelonephritis and reveal structural abnormalities that increase the risk for UTIs.

Treatment of infection should be based on the suspected site of infection, something that can be difficult given the atypical presentation of infection. Shorter durations (i.e., 5 to 7 days) are recommended for lower tract infection; pyelonephritis should be treated with 14 days of antibiotics, and relapsed/recurrent infection with the same organism warrants prolonged treatment (>4 weeks). The choice of antimicrobial should consider the potential for resistance, the severity of illness, and drug interactions, especially with immunosuppressive agents; IV therapy should be initiated for more severe infections. Patients with frequent or persistent UTIs should be assessed for structural abnormalities and surgical interventions considered as appropriate. A significant area of controversy has been the management of asymptomatic bacteriuria. A recent prospective trial of treatment of asymptomatic bacteriuria commencing 2 months posttransplant failed to show a benefit from treating asymptomatic bacteriuria and current guidelines do not recommend treating these patients, especially given the potential risk for adverse events including increased antibacterial resistance and C. difficile. The optimal management of patients with recurrent infections is unknown. Correction of structural and functional abnormalities should be performed. Postmenopausal women may benefit from vaginal estrogen and urinary acidification also has been employed. Chronic or prolonged antimicrobials should be reserved for recipients who have had more complicated courses since there is a significant potential for adverse effects from antibiotics.

Prevention

Successful transplantation is more likely when candidates are carefully evaluated for infection risk before transplant. That includes assessing their home and work environments, including prior living arrangements, their personal contacts, pets, and their hobbies. Because of the potential for TB and endemic diseases such as coccidioides and strongyloides to reactivate after the transplant, it is important to evaluate patients for diseases that may have been acquired earlier due to residence in areas where these infections were endemic. Especially important is the need to evaluate candidates for TB, because this infection may reactivate after transplant and diagnosis and treatment is complicated by immunosuppressive therapy. This should include taking a thorough history, obtaining chest radiography, and performing either an intra-dermal skin test using PPD or an IGRA. Given the reduced sensitivity of these tests in patients with CKD, it is important to assess the individual’s risk for infection by taking a careful history and reviewing chest radiography for signs of prior infection. Patients who have evidence of latent TB who have not completed prior prophylactic therapy should be treated with 9 months of isoniazid either before or after transplant. Shorter-course rifampicin containing regimens can be considered in the pretransplant setting if there are no significant drug interactions that will prevent its use.

Immunization

One especially important intervention in the pretransplant setting is the review and updating of vaccine status. Given the potentially reduced immunogenicity and efficacy of vaccines administered after transplant and the increased risk for transplant recipients for vaccine-preventable infections, this is especially important. Recommended vaccines are included in Table 40.3. Hepatitis B vaccine is especially important for patients who are listed for transplantation since there is an increased risk for transmission in dialysis centers and patients who are immune may be more safely transplanted with kidneys from donors with a history of hepatitis B or those at increased risk for new hepatitis B infections. Patients with
CKD should receive a double dose of the recombinant vaccine and hepatitis B surface antibody levels should be measured following completion of the vaccine series.\textsuperscript{182} Historically, there have been some concerns regarding an increased risk for rejection after influenza vaccine due to the development of low level \textit{de novo} anti-HLA antibodies after immunization.\textsuperscript{183} However, the linkage of vaccination to rejection has not been demonstrated and a study examining Medicare claims data in the first year after kidney transplant demonstrated that influenza vaccination was associated with reduced allograft loss and death.\textsuperscript{184} Ideally, all vaccines should be updated before transplantation; however, nonlive virus vaccines may be safely administered after transplant.\textsuperscript{181} If possible, it may be advisable to delay posttransplant immunization for 6 months to improve vaccine response; if a patient is transplanted immediately before influenza season, vaccines may be given sooner after transplant. Because transplant recipients may have suboptimal vaccine responses, it is important to vaccinate household contacts as well. CKD and transplantation have both been associated with reduced vaccine responsiveness; these individuals should receive conjugate pneumococcal vaccine followed by the pneumococcal polysaccharide capsule vaccine to maximize vaccine response.\textsuperscript{185} Vaccine schedules are updated annually; it is important to review to ensure appropriate immunizations are administered.\textsuperscript{186}

Although kidney transplant recipients are at increased risk for infection, careful consideration of specific infection risks, implementation of preventive measures, and early recognition of infections may mitigate this risk. Given the ever-changing nature of transplantation, ongoing consideration of preventive strategies, including antimicrobials, immunization, and environmental assessments and utilization of directed diagnostic strategies for prompt recognition of infection is essential to optimize posttransplant outcomes.

\textbf{A full list of references is available at www.expertconsult.com.}
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