



Infection in Kidney Transplantation

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Abstract

Infection is an important cause of morbidity and mortality after kidney transplantation. It has been estimated that 70% of kidney transplant recipients will experience an infection episode within the first 3 years after transplantation (Dharmidharka et al. 2007). After cardiovascular disease, infection is the second leading cause of death in recipients with allograft function (Snyder et al. 2009). The immunosuppressive therapy required to prevent organ rejection places the kidney transplant recipient at increased risk for donor-derived, nosocomial, and community-acquired infections as well as reactivation of latent pathogens. Pretransplant screening, immunizations, and optimal antibacterial and antiviral prophylaxis can help to reduce the impact of infection. Awareness of the approach to infection in the transplant recipient including diagnostic and management strategies is essential to optimizing outcomes.

Keywords

Renal transplant · Solid organ transplant · Immunocompromised host · Viral · Bacterial · Fungal · Atypical infections

Introduction

A total of 17,600 kidney transplants were performed in the United States in 2013. As the incidence of acute rejection has declined, the probability of graft and patient survival continues to improve (USRDS 2015). Infection, however, remains an important cause of morbidity and mortality after kidney transplantation. It has been

estimated that 70% of kidney transplant recipients will experience an infection episode within the first 3 years after transplantation (Dharmidharka et al. 2007). After cardiovascular disease, infection is the second leading cause of death in recipients with allograft function (Snyder et al. 2009). The immunosuppressive therapy required to prevent organ rejection places the kidney transplant recipient at increased risk for donor-derived, nosocomial, and community-acquired infections as well as reactivation of latent pathogens.

Infection Timeline

The kidney transplant recipient's net state of immune suppression and epidemiologic exposures determine the risk for infection at a given time. A traditional timeline has been used to predict patterns of infection after organ transplantation. This timeline has been altered in recent years with changes in immunosuppressive therapy and the routine use of antibacterial and antiviral prophylaxis. Treatment for acute rejection and coinfection with viruses such as Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) may also alter predictable patterns of infection (Fishman 2007).

The basic concepts of the traditional timeline, however, are still used to establish a differential diagnosis for infection at varied intervals post-transplantation (Fig. 1). Within the first month, infections are noted to include those related to surgical complications, nosocomial exposures, and donor-derived pathogens. Multidrug-resistant organisms including Methicillin-resistant *Staphylococcus aureus* (MRSA), Vancomycin-resistant *Enterococcus* (VRE), and Carbapenem-resistant enterobacteriaceae (CRE) are important considerations, as is *Clostridium Difficile*. Urinary tract

<u>< 1 month</u>	<u>1-6 months</u>	<u>> 6 months</u>
-Nosocomial infection	-Donor derived infection	-Community acquired pneumonia
-Technical, anastomotic complications	-Urinary tract infection	-Influenza
-Infection with antibiotic resistant organisms (MRSA, VRE, CRE)	-Adenovirus	-Urinary tract infection
- <i>Clostridium difficile</i> colitis	-Influenza	-Late onset CMV
-Donor derived infection	-Polyoma virus BK	-EBV (PTLD)
	-HCV	-HBV, HCV
	- <i>Mycobacterium tuberculosis</i>	-JC polyoma virus (PML)
	-Endemic mycoses	-Aspergillus, Mucormycosis
	Without PJP and <u>antiviral prophylaxis</u>	-Nocardia species
	-Pneumocystis	
	-Herpesvirus infection (CMV, HSV, VZV, EBV)	
	-HBV	

Fig. 1 Timeline of infection after kidney transplantation

infections are common within the first 6 months. Opportunistic infections are more likely to occur 1–6 months after transplantation, reflecting the greater impact of immune suppression during this time. Reactivation of latent pathogens such as polyoma virus BK, hepatitis C virus (HCV), and *Mycobacterium tuberculosis* may also occur. Prophylaxis for *Pneumocystis jiroveci*, herpes viruses including CMV, and hepatitis B virus (HBV) makes these infections less common during this time period. Beyond 6 months, the degree of immune suppression for most patients decreases. Risk remains, however, for community-acquired infection, environmental exposures, recurrent infection, and the late presentation of viral infection, in particular CMV, once prophylaxis has been discontinued (Fishman 2007; Karuthu and Blumberg 2012).

Pretransplant Screening

Interventions can be undertaken to reduce the impact of infection after kidney transplantation. Pretransplant screening of donors and recipients for infection that can be transmitted with organ donation or reactivated in an immune suppressed recipient is essential for optimizing transplant outcomes. Guidelines for pretransplant screening are available from the American Society for Transplantation (Fischer et al. 2013), Kidney Disease: Improving Global Outcomes (KDIGO 2009) and the US Public Health Service (Seem et al. 2013). Recommended screening tests for donors and recipients are listed in Table 1.

Screening of living donors is performed prior to transplantation with varied timing. If there is a

Table 1 Pretransplant screening

Pathogen and test	Donor status	Recipient status	Recommendation
HIV: Anti-HIV ½ or HIV Ag/Ab combination assay and HIV NAT	HIV(+)	HIV(-)	Reject
	HIV(-)	HIV(+)	Consider if HIV is well controlled
	HIV(+)	HIV(+)	Consider if HIV is well controlled
HCV: Anti-HCV and HCV NAT	HCV(+)	HCV(-)	Reject, may be a consideration in the future
	HCV(-)	HCV(+)	Consider, HCV(+) candidates should have a liver biopsy, improved outcomes if HCV is treated pretransplant
	HCV(+)	HCV(+)	Consider (as for D-/R+)
HBV: HBsAg, HBsAb and HBcAb (IgM/IgG); HBV NAT (center dependent)	sAg(-), cAb(-)	sAg(-), cAb(+), sAb(+/-)	Accept, vaccinate sAb(-) candidates
	sAg(+/-), cAb(+/-)	sAg(+), cAb(+)	Consider, with prophylaxis posttransplant
	sAg(-), cAb(+)	sAg(-), cAb(+/-), sAb(+/-)	Accept if donor is cIgM(-) and vaccinate sAb(-) candidates, offer prophylaxis posttransplant if sAb(-) or lost; reject if donor is cIgM(+)
	sAg(+), cAb(+)	sAg(-), cAb(+/-), sAb(+/-)	Reject
CMV IgG	CMV(+) or (-)	CMV(+)	Accept; will need posttransplant prophylaxis or preemptive therapy
	CMV(+)	CMV(-)	Accept; high risk for CMV infection, will need posttransplant prophylaxis
EBV IgG	EBV(+) or (-)	EBV(+)	Accept
	EBV(+)	EBV(-)	Accept; at risk for primary EBV and PTLN, monitor posttransplant
HSV 1/2 IgG	HSV(+)	HSV(+) or (-)	Accept; Acyclovir prophylaxis used for CMV D-/R-
HTLV 1/2 antibody (optional)	HTLV ½(+)	HTLV ½(-)	Reject if HTLV 1+; need Western blot testing or NAT to distinguish HTLV 1 from 2
VZV antibody	NA	VZV-	Vaccinate prior to transplant
RPR, VDRL	RPR or VDRL(+)	RPR or VDRL(+/-)	Accept; recipient will need treatment with penicillin if donor or recipient tests positive and is confirmed with a treponemal-specific test and not treated
<i>Toxoplasma gondii</i> IgG	Toxoplasma(+/-)	Toxoplasma(+)	Accept; TMP/SMX prophylaxis posttransplant
	Toxoplasma(+)	Toxoplasma(-)	Accept; TMP/SMX prophylaxis posttransplant
Tetanus, diphtheria and acellular pertussis	NA	Confirm vaccination history	Vaccinate candidates if not vaccinated as adult
<i>Streptococcus pneumoniae</i>	NA	Confirm vaccination history	Vaccinate candidates prior to transplant

(continued)

Table 1 (continued)

Pathogen and test	Donor status	Recipient status	Recommendation
Measles, mumps and rubella	NA	MMR titer	Vaccinate candidates if titer(−) (not to be given posttransplant)
Influenza	NA	Confirm vaccination history	Vaccinate candidates annually
<i>Mycobacterium tuberculosis</i> : PPD or interferon-gamma release assay	Screen <i>live</i> donor PPD or interferon-gamma release assay(+)	PPD or interferon-gamma release assay(+)	Evaluate for active TB in any (+) live donor or candidate; delay transplant until active TB is treated; recipient can complete treatment for latent TB after transplant
CNS viral pathogens (e.g. LCMV, rabies, WNV)	Clinical suspicion	NA	Reject
<i>Strongyloides stercoralis</i> IgG (based on exposure, prevalence of infection in region)	Screen <i>live</i> donor Strongyloides(+)	Strongyloides (+/−)	Treat (+) donor or recipient with Ivermectin prior to transplant
West Nile virus NAT (based on exposure, prevalence of infection in region)	Screen <i>live</i> donor: WNV NAT(+)	NA	Reject
	Screen <i>deceased</i> donor: Unexplained febrile or neurologic illness(+)	NA	Reject
Zika virus, also consider dengue virus and chikungunya virus (based on history of exposure, prevalence of infection in region)	Zika infection(+)	NA	Defer transplant
	Travel to Zika area in past 28 days(+)	NA	Defer transplant The risk of Zika transmission should be balanced with the benefit of the transplant
Endemic mycoses <i>Coccidioides</i> IgM/IgG, <i>Histoplasma</i> Ab (based on exposure, prevalence of infection in region)	Screen <i>live</i> donor <i>Coccidioides</i> or <i>Histoplasma</i> (+)	<i>Coccidioides</i> or <i>Histoplasma</i> (+)	Treat donor or recipient with active infection prior to transplant. Consider prophylaxis posttransplant if donor or recipient has latent infection

significant delay (more than 28 days) between screening and the time of transplant, living donors should be re-evaluated to rule-out recently acquired infection. The CDC recommends that all living donors be rescreened for human immunodeficiency virus (HIV) prior to donation to exclude recent infection (CDC 2011). Repeat screening for HCV and HBV may also be indicated if risk factors for infection are identified (Fischer et al. 2013).

Deceased donor screening, in contrast, is under time constraints and is usually performed within hours of transplantation in coordination with organ procurement organizations. Infection with HIV, HBV, and HCV may not be detected in the early stages of infection. Many transplant centers now perform more sensitive rapid molecular testing on

potential organ donors including nucleic acid amplification (NAT) testing for HIV, HBV, and HCV. A comprehensive medical and social history on potential organ donors is required in order to identify risk factors for blood borne pathogens. In efforts to expand the pool of available organs, recipients may consent to receipt of a kidney from a NAT negative donor who is deemed “high risk” for blood borne infection based on identified risk factors. Recipients of such organs are monitored posttransplantation with testing for HIV, HBV, and HCV between 1 and 3 months and for HBV again at 12 months (Fischer et al. 2013; Seem et al. 2013; Kovacs et al. 2014; Len et al. 2014). Use of HCV- and HBV-positive organs can be considered in respective positive recipients. Furthermore, in 2013 the HIV Organ Policy Equity

Act lifted a long-standing ban on allowing HIV-positive organs to be donated to HIV-positive recipients (Mgbako et al. 2013; Muller et al. 2015).

Donors who have active bacterial infection at the time of kidney procurement may transmit infection to the recipient. Screening for bacterial infection in kidney donors includes assessing for urinary tract infection and bacteremia. Urine and blood culture data are reviewed. If a kidney donor is known to have a urinary tract or systemic infection with a virulent organism such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, or *Candida* species, the organ recipient is usually treated with a 10–14 day course of targeted antimicrobial therapy since these bacteria can compromise vascular and urinary anastomoses leading to mycotic aneurysms, anastomotic, and organ failure (Fischer et al. 2013). Allograft contamination can occur during organ procurement or processing. Interpretation of organ preservation fluid cultures is challenging. The risk of transmission of infection to the organ recipient from contaminated preservation fluid, however, is low (Fischer et al. 2013; Len et al. 2014).

Vaccinations

Candidates for kidney transplantation should have their vaccine status reviewed and updated in accordance with recommendations issued by the Advisory Committee on Immunization Practices with the Centers for Disease Control and Prevention (CDC 2012). While vaccinations in end stage renal disease patients may be less effective and durable than in healthy patients, a better response can be anticipated prior to transplantation than after (Janus et al. 2008; Kausz and Pahari 2004).

Special consideration should be given to vaccination for pneumococcus, influenza, and HBV. Two pneumococcal vaccines are currently licensed for use in the United States: the 13-valent pneumococcal conjugate vaccine (PCV 13, Prevnar 13) and the 23-valent-pneumococcal-polysaccharide vaccine (PPSV 23, Pneumovax 23). Current guidelines recommend that unvaccinated patients with chronic renal failure receive PCV 13 followed at least 8 weeks later by PPSV 23 (Kobayashi et al.

2015). A second dose of PPSV 23 is recommended 5 years after the first dose (CDC 2012). Influenza vaccination should be administered annually. There are a number of influenza vaccine formulations available. Live attenuated influenza vaccination (FluMist) is not recommended in chronic kidney disease patients. An inactivated vaccine option should be used (CDC 2012). A high dose inactivated influenza vaccine is now available and was shown to induce a higher antibody response than traditional vaccines in adults over the age of 65 (Diaz-Granados et al. 2014). The use of this vaccine in transplant candidates and recipients is currently under investigation. Transplant candidates not immune to HBV should receive high dose HBV vaccination (40 micrograms antigen per dose) due to decreased response rates with standard dosing (Huprikar et al. 2015).

Viral Infections

Cytomegalovirus Infection

Human cytomegalovirus-human herpes 5 (CMV), a member of the family Herpesviridae, is an opportunistic pathogen occurring in 20–60% of solid organ transplant recipients (Brennan 2001). CMV is a cause of significant morbidity and mortality in this population (Mwintshi and Brennan 2007). The incidence of CMV in the renal transplant population is estimated to be between 8% and 32% (Patel and Paya 1997). Renal transplant patients are at lower risk for primary CMV compared with other organ transplant recipients owing to a lower burden of latent virus in renal allograft tissue.

The risk factors for development of CMV disease include donor seropositivity/recipient seronegativity (D⁺/R⁻), use of induction immunosuppression (antilymphocyte antibodies), donor age >60 years, simultaneous kidney-pancreas transplantation, treatment for acute rejection, impaired transplant function, and concurrent infection from other viruses (like EBV and HHV-6 and 7) (De Keyzer et al. 2011). CMV-seronegative recipients of CMV-seropositive donors (D⁺/R⁻) are at the highest risk, whereas D⁺/R⁺ or D⁻/R⁺ transplantations are

considered to be moderate risk with D⁻/R⁻ being lowest risk, with an incidence of CMV disease <5% (De Keyzer et al. 2011). Immunosuppressive drugs also influence the incidence and severity of CMV disease. For instance, cyclosporine increases the risk of CMV disease, whereas use of sirolimus seems to have a protective effect (San Juan et al. 2008). The use of antilymphocyte antibody (antithymocyte globulin or muromonab-CD3) is associated with a two to fivefold increase in the rate of CMV, but basiliximab and daclizumab do not seem to increase its incidence (De Keyzer et al. 2011).

CMV infection may occur in solid organ transplantation recipients as primary infection when a CMV seronegative individual receives cells latently infected with CMV from a seropositive donor, donor-derived reinfection, or reactivation of latent recipient infection (Patel and Paya 1997). The following definitions are commonly used in the transplant literature to differentiate CMV infection from CMV disease. CMV infection is evidence of CMV replication regardless of symptoms, and CMV disease is evidence of CMV infection with symptoms, such as viral syndrome, leukopenia, thrombocytopenia, or invasive tissue disease (e.g., pneumonitis, hepatitis, retinitis, gastrointestinal disease) (Humar and Snyderman 2009). CMV disease and even asymptomatic CMV infection have been shown to be independent risk factors for reduced graft survival and overall mortality beyond 100 days posttransplantation (Sagedal et al. 2004). Infection with CMV has been implicated in acute allograft dysfunction and chronic allograft nephropathy (McLaughlin et al. 2002; Tong et al. 2002). CMV disease is also associated with posttransplant lymphoproliferative disorder (PTLD), posttransplant diabetes mellitus, and transplant artery stenosis (Pouria et al. 1998; Hjelmessaeth et al. 2004; Manez et al. 1997).

CMV infection can occur as acute infection between the first and 6 months following transplant, when immunosuppression is at its maximum or as delayed infection from reactivation of latent virus after antiviral prophylaxis has completed, later in the first year. Given the significant effect of CMV on patient outcomes, prevention plays an important role. Serologic screening for

CMV should be performed on both donor and recipient prior to transplant to categorize high risk patients. Several CMV vaccine candidates are under investigation although none are currently available. Universal prophylaxis involves giving antivirals to those recipients at risk posttransplant before the onset of infection, whereas in preemptive therapy patients are monitored at regular intervals and started on antivirals when there is early evidence of replication prior to onset of clinical disease. Chemoprophylaxis in high risk patients (D⁺/R⁻) has shown to reduce the incidence of CMV disease by 60% and has decreased CMV associated mortality and opportunistic infection (Hodson et al. 2005). Preemptive therapy in high risk patients based on CMV viral load monitoring has not shown reduction in acute rejection or all-cause mortality (Strippoli et al. 2006). A randomized controlled trial by Kliem et al. in 2008 comparing oral ganciclovir chemoprophylaxis with viral load monitoring revealed improved graft survival in those who received ganciclovir chemoprophylaxis (Kliem et al. 2008). A recent Cochrane review from 2013 concluded that the efficacy of preemptive therapy compared with prophylaxis to prevent CMV disease remains unclear due to significant heterogeneity between studies and that additional head-to-head studies are required to determine the relative benefits and harms of preemptive therapy and prophylaxis to prevent CMV disease in solid organ transplant recipients (Owers et al. 2013).

Standard prophylactic guidelines recommend therapy in D⁺/R⁻, D⁺/R⁺, and D⁻/R⁺ using oral ganciclovir or valganciclovir for a minimum of 3 months posttransplant and 1–3 months after treatment of rejection with antilymphocyte therapy (Humar and Snyderman 2009; Kotton et al. 2013). Valganciclovir has replaced ganciclovir because of better bioavailability, lower pill burden, and reduced availability of oral ganciclovir (Paya et al. 2004). The optimal length of prophylaxis is unknown, but recent trials have shown that 6 months of prophylaxis is more effective in decreasing the incidence of CMV disease in D⁺/R⁻ kidney transplant recipients (Humar et al. 2010; Doyle et al. 2006). Current guidelines recommend dosing valganciclovir at 900 mg daily

(adjusted for renal dysfunction) if tolerated in D+/R– recipients. Some centers have successfully treated patients with half of this dose (450 mg daily) with less drug toxicity. However, D+/R– recipients may be at higher risk of breakthrough infection and the development of resistance with this lower dosing strategy (Kotton et al. 2013).

The diagnosis of CMV disease can be made by several techniques including CMV antigenemia assay, nucleic acid testing (NAT), serology, antibody testing, viral culture, and histopathology. NAT is generally more sensitive than antibody testing or culture. Higher values by NAT are suggestive of CMV disease and weekly viremia testing can be used to monitor response to therapy. The interlaboratory variability of NAT is expected to be reduced with the recent establishment of international standards, intended to be used in the standardization of nucleic acid amplification technique (NAT)-based assays for HCMV (Karuthu and Blumberg 2012). Patients with gastrointestinal and neurologic CMV disease often fail to exhibit CMV viremia and histopathology is necessary to establish diagnosis in these instances.

Treatment of active CMV disease requires a combination of immunomodulation, antiviral therapy with or without adjuvant therapy and if possible, reduction of immunosuppression (Kotton et al. 2013; Green et al. 2004). The mainstay of therapy is intravenous ganciclovir. The VICTOR trial (Valcyte in CMV Disease Treatment of Solid Organ Recipients) demonstrated oral valganciclovir was not inferior to intravenous ganciclovir in mild to moderate CMV disease in solid organ transplant recipients (Asberg et al. 2009). The current guidelines recommend renally adjusted intravenous ganciclovir 5 mg/kg twice daily or oral valganciclovir, 900 mg twice daily for mild CMV disease (Kotton et al. 2013). In severe CMV disease, intravenous ganciclovir is preferred with reduction of immunosuppression despite the increased risk of rejection (De Keyzer et al. 2011). The use of adjuvant therapy with CMV-specific hyperimmune globulin or standard intravenous immunoglobulin may be considered in individuals with hypogammaglobulinemia, severe systemic infection, or in failure to respond to standard therapy (Humar et al. 2010).

CMV resistance to ganciclovir has been noted in renal transplant recipients due to mutations in UL 97, the gene responsible for the first phosphorylation step in ganciclovir activation and UL 54, the gene responsible for DNA polymerase (Limaye et al. 2000). CMV resistance should be considered when patients have worsening disease or persistent, unchanged viremia at 2 weeks of therapy and in such cases, genotype testing for mutations of the genes encoding UL 97 and UL 54 should be performed (Weikert and Blumberg 2008). Treatment options for drug resistant CMV include the use of high dose ganciclovir, foscarnet, and cidofovir; however, no clinical trial data are available regarding optimal therapy options for resistant CMV. The use of novel agents including leflunomide and artesunate has been attempted as salvage therapy with varying success. Several new antiviral treatment options are currently under investigation including maribavir and brincidofovir (an oral prodrug of cidofovir with less nephrotoxicity) for use in the treatment of drug resistant CMV (Limaye et al. 2000).

Epstein Barr Virus Infection

Epstein Barr Virus – Human herpesvirus 4 (EBV) is a ubiquitous gamma herpes virus that remains latent in lymphocytes following primary infection. It is responsible for posttransplant lymphoproliferative disorder (PTLD) which increases morbidity and mortality in the transplant population. Approximately 62–79% of PTLT cases have been associated with EBV (Karuthu and Blumberg 2012). PTLT most commonly occurs in the first year posttransplant (Cockfield et al. 1993). The risk factors for PTLT include EBV naïve recipients who receive EBV seropositive organs, active primary EBV infection, younger recipient, coinfection by CMV and other viruses, prior splenectomy, second transplant, acute or chronic graft versus host disease, immunosuppressive drug regimen (OKT3 or polyclonal antilymphocyte antibody), and the type of organ transplanted. Kidney transplant recipients are at lower risk compared with other types of transplants and have an incidence

of approximately 1–3% (Gulley and Tang 2010; Allen et al. 2009; Taylor et al. 2005).

The majority of symptomatic EBV infections in renal transplant recipients are primary infection likely related to transmission of donor virus. EBV disease can be asymptomatic or presents with a nonspecific febrile syndrome, lymphadenopathy, hepatosplenomegaly, atypical+ lymphocytosis, hematologic disorders including anemia, leukopenia, thrombocytopenia, and organ-specific diseases like gastroenteritis, hepatitis, or pneumonitis (Allen et al. 2009). PTLD typically follows primary infection and frequently presents as a rapidly enlarging mass in the grafted organ, lymph nodes, bone marrow, or extranodal sites (Manez et al. 1997). PTLD is divided into four major histopathologic subtypes as per the World Health Organization (WHO): early lesions, polymorphic PTLD, monomorphic PTLD, and classical Hodgkin lymphoma type PTLD.

Definitive diagnosis of PTLD requires histopathologic confirmation by tissue excision biopsy with immunologic cell typing, cytogenetics, immunoglobulin gene rearrangements, and EBV-specific staining (Allen et al. 2009). Staging is performed by histologic types (monoclonal versus polyclonal, T cell versus B cell) and location (allograft, other organs, metastasis) (Weikert and Blumberg 2008). Clinical management of PTLD typically involves reduction of immunosuppression which can lead to remission in 23–86% of the patients (Weikert and Blumberg 2008). Antiviral therapy with acyclovir or ganciclovir is controversial and no evidence supports its efficacy (Taylor et al. 2005). Rituximab (monoclonal antibody to CD20) is commonly used for treatment of PTLD in recipients who failed reduction of immunosuppression alone (Allen et al. 2009). In isolated graft PTLD, surgical resection is an option (Weikert and Blumberg 2008). In patients that fail the above strategies, IFN and IVIG have been used with varying success and cytotoxic chemotherapy with radiation remains salvage therapy (Green et al. 2004).

There is no standardized therapy to prevent PTLD. KDIGO guidelines recommend monitoring EBV viral load in high risk renal transplant patients within the first week after transplant, then at least monthly for 3–6 months and then every 3 months

for the rest of the first posttransplant year. Additional viral load monitoring is recommended after treatment for acute rejection in high risk groups (children, EBV D+/R–). Outcomes with PTLD in renal transplant patients vary according to the site involved. Patients with isolated graft involvement have a 5-year survival of 68% compared with those patients with PTLD extending beyond the allograft whose survival varied between 36% and 38% (Weikert and Blumberg 2008).

Herpes Simplex Virus and Varicella Zoster Virus Infection

Human herpesvirus 1 – herpes simplex virus types 1 and 2 (HSV) – and Human herpesvirus 3 – varicella zoster virus (VZV) – are alpha herpes viruses. HSV 1 has a seroprevalence of 60% in the adult population, while HSV 2 has a seroprevalence of 15% and VZV rates can be as high as 90% (Green et al. 2004). The incidence of HSV disease in renal transplant recipients is approximately 53% and VZV 4–12% (Patel and Paya 1997).

HSV may cause primary infection following which the virus remains latent in the sensory nerve ganglia or more commonly causes reactivation infection. HSV may be seen as early as in the first posttransplant month in the absence of prophylaxis. HSV infection usually presents with oral or genital mucocutaneous lesions, occasionally pneumonitis, tracheobronchitis, esophagitis, hepatitis, encephalitis, or disseminated infection (Green et al. 2004). VZV causes localized dermatomal or multidermatomal or disseminated zoster with or without visceral involvement (pneumonitis, hepatitis, pancreatitis, encephalitis).

Pretransplant screening for prior VZV infection should be performed, and naïve patients should be vaccinated with live attenuated varicella vaccine before transplant whenever possible in order to avoid primary VZV infection posttransplantation (Fehr et al. 2002). Since VZV is a live vaccine, it should not be given if transplant is expected within 4–6 weeks in order to avoid active shedding of virus at the time of transplant. Posttransplant prophylaxis is recommended with acyclovir, valacyclovir, or ganciclovir (in those

who need CMV prophylaxis) for approximately 1–3 months posttransplant in order to avoid HSV and VZV reactivation (Green et al. 2004).

Diagnosis of HSV and VZV infection can be made with PCR or direct fluorescence antibody for HSV from vesicular lesions, CSF, or visceral tissue samples. Serologies are rarely helpful in active infection owing to high seroprevalence. KDIGO guidelines recommend that renal transplant recipients who develop less severe HSV or VZV infections can be treated with an appropriate oral antiviral agent (e.g., acyclovir, valacyclovir, or famciclovir), and those with systemic infection should be treated with intravenous acyclovir and a reduction in immunosuppressive medication and subsequently switched to an appropriate oral antiviral agent (Green et al. 2004). The use of foscarnet, cidofovir, or topical trifluridine may be considered in patients with acyclovir resistant virus with careful monitoring of renal functions (Kotton and Fishman 2005; Tan and Goh 2006).

Human Herpesvirus 6, Human Herpesvirus 7, and Human Herpesvirus 8 Infection

Human herpesvirus 6 and human herpesvirus 7 (HHV 6 and HHV 7) are ubiquitous with high seroprevalence in adults. These viruses are common causes of fever in children and remain latent in lymphocytes following primary infection. HHV 6 uses the CD46 molecule as its receptor but may also infect other cell types, such as monocytes, and epithelial and endothelial cells. HHV 7 uses the CD4 molecule as its receptor and is more strictly lymphotropic. Infection occurs as a result of reactivation in the first 4 weeks following transplant often in recipients not on CMV prophylaxis (Singh and Carrigan 1996). Clinical manifestations include fever, rash, hepatitis, interstitial pneumonitis, encephalitis, leukopenia, and myelosuppression. Owing to its immunomodulatory effects, it is hypothesized that HHV 7 may act as a cofactor for HHV 6 and CMV reactivation, while both HHV 6 and HHV 7 may act as cofactors in the pathogenesis of CMV disease and

acute rejection (Kidd et al. 2000; Chapenko et al. 2000; Dockell and Paya 2001). The diagnosis of HHV 6 and HHV 7 is made by tissue immunohistochemistry or NAT testing of peripheral blood lymphocytes. Treatment includes reduction in immunosuppression and ganciclovir, but cidofovir and foscarnet have also been utilized (Green et al. 2004; Kotton and Fishman 2005; Dockell and Paya 2001).

HHV 8 is associated with primary effusion lymphoma, Kaposi's sarcoma, and multicentric castlemann's disease. Infection can be acquired as primary through the allograft or through reactivation of latent virus (Diociaiuti et al. 2000; Regamy et al. 1998). HHV 8 causes Kaposi's sarcoma, the most common presentation in renal transplant recipients, through upregulation of vascular endothelial growth factor (VEGF) receptor F1 K1/KDR in endothelial cells (Stallone et al. 2005). Treatment includes reduction in immunosuppression and cytotoxic chemotherapy. Sirolimus, an immunosuppressive drug used in renal transplant patients is thought to inhibit not only the production of VEGF but also dampens its effect on endothelial cells (Stallone et al. 2005).

BK and JC Virus Infection

BK polyomavirus (BKV) and JC polyomavirus (JCV) belong to the family Polyomaviridae. BKV is responsible for causing polyomavirus associated nephropathy (PVAN) in 95% of cases and JCV in less than 5% of the cases. PVAN occurs in 1–10% of patients with renal transplantation and causes renal allograft loss in 10–80% of cases (Drachenberg et al. 2005; Dadhania et al. 2008).

The risk factors for BKV associated PVAN include the use of potent immunosuppressive regimens, Caucasian race, older age, diabetes mellitus, cadaveric renal transplant, and combined kidney and pancreas transplant (Hirsch et al. 2005; Trofe et al. 2003). BKV is known to cause interstitial nephritis, ureteral stenosis, and ureteral stricture of the allograft kidney most commonly occurring within the first 3–4 months after renal transplant patients when immunosuppression is at

its highest (Randhawa and Brennan 2006). JCV less commonly causes PVAN and is more frequently associated with Progressive Multifocal Leukoencephalopathy (PML), a demyelinating disorder of the white matter presenting as neurologic impairment and dementia (Phillips et al. 2004).

Diagnosis of BKV includes the use of viral load assays (blood, urine), detection of viral cytopathic effect (decoy cells), NAT, BKV-specific antibody, or histopathology (Hariharan 2006). KDIGO guidelines recommend screening all renal transplant recipients for BKV with quantitative plasma NAT at least monthly for the first 3–6 months after transplantation, then every 3 months until the end of the first posttransplant year, whenever there is an unexplained rise in serum creatinine, and after treatment for acute rejection. The guidelines suggest reducing immunosuppressive medications when BKV plasma NAT is persistently greater than 10,000 copies/ml (107 copies/l) (KDIGO 2009). Sustained high BK viremia in spite of reduction in immunosuppression may need additional antiviral therapy, although data regarding optimal treatment options are unknown. There are limited data regarding the effectiveness of leflunomide and/or cidofovir or the use of fluoroquinolones or IVIG for treatment of BKV infection (Randhawa and Brennan 2006; Josephson et al. 2006). To date there is no effective treatment for PML. Patients with allograft loss due to PVAN have undergone successful retransplantation (Hariharan 2006).

Hepatitis B and C Virus Infections

Patients with chronic renal failure, in particular those receiving hemodialysis, are at increased risk for contracting hepatitis B virus (HBV). The prevalence of hepatitis B surface antigen (HBsAg)-positive patients has declined because of HBV vaccination, strict segregation of HBsAg-positive patients in dialysis units, improved screening of blood products, and the use of erythropoiesis stimulating agents (Karuthu and Blumberg 2012). Approximately 2–10% of patients with a history of HBV prior to transplant will reactivate

posttransplant (Weikert and Blumberg 2008). Serial monitoring of HBV DNA every 3–6 months is required after transplantation as liver enzyme levels do not reflect infection status and elevated viral loads suggest resistance to therapy (Levitsky et al. 2013). In a meta-analysis conducted by Fabrizi and his colleagues, HBsAg seropositivity was an independent risk factor for allograft loss and posttransplant death (Fabrizi et al. 2005). The treatment options currently approved for chronic HBV include: IFN alpha, pegylated IFN, lamivudine, entecavir, telbivudine, tenofovir, and adefovir (Fabrizi et al. 2005; Chan et al. 2002; Chang et al. 2010). KDIGO recommends that interferon treatment generally be avoided because of the high associated incidence of rejection. Tenofovir or entecavir are preferable to lamivudine, to minimize the development of drug resistance, unless medication cost requires that lamivudine be used. During therapy with antivirals, HBV DNA and ALT levels should be measured every 3 months to monitor efficacy and to detect drug resistance. All HBsAg-positive renal transplant recipients should receive prophylaxis with tenofovir, entecavir, or lamivudine. HBsAg-positive patients with cirrhosis should be screened for hepatocellular carcinoma every 12 months with liver ultrasound and alpha fetoprotein. Patients who are negative for HBsAg and have HBsAb titer <10 mIU/ml should receive booster vaccination to raise the titer to >100 mIU/ml (KDIGO 2009).

Hepatitis C virus (HCV) infection has been increasingly recognized in end stage renal disease patients (ESRD). Donor-derived HCV may uncommonly occur after transplantation. Screening of patients with ESRD and testing renal transplant patients for newly acquired HCV should include NAT (Levitsky et al. 2013). HCV-positive donors can be considered for HCV-positive recipients and possibly will be considered for HCV-negative recipients in the future given improved treatment options for cure of HCV that could be administered post transplant. HCV-infected renal transplant recipients have decreased survival and increased complication rates. Posttransplant complications include glomerulonephritis (GN), posttransplant diabetes mellitus, and accelerated progression to cirrhosis with fibrosing cholestatic hepatitis (Morales et al.

2010). Liver biopsy within 6–12 months of transplantation and subsequent biopsies are required for evaluation of liver disease posttransplant as 20–51% of patients may have normal liver enzyme levels with abnormal histologic features (Ashry Ahmed Gheith 2011). HCV-infected recipients should be tested for proteinuria every 3–6 months, and patients with new onset proteinuria should undergo allograft biopsy (KDIGO 2009).

The effect of immunosuppression on the progression of HCV-related liver injury and the management of immunosuppression in the HCV-infected renal transplant recipient remain uncertain. Thus, it is preferable to treat HCV in transplant candidates prior to transplantation given the potential for improved outcomes with successful HCV treatment and the complications associated with treatment posttransplant. Patients with a sustained virologic response to pretransplant treatment have a reduced risk for HCV recurrence and decreased posttransplant GN (Dominguez-Gil and Morales 2009). Options for treatment include interferon/peginterferon alone or in combination with ribavirin. The risk of toxicity with the addition of ribavirin has limited the use of combination therapy in chronic kidney disease (CKD) patients. The availability of direct acting HCV protease and polymerase inhibitors has sparked new enthusiasm for treating HCV-infected CKD patients and studies are ongoing evaluating the use of these agents in CKD. If treatment cannot be given prior to transplant, KDIGO recommends monotherapy with standard interferon for HCV-infected renal transplant recipients in whom the benefits of antiviral treatment clearly outweigh the risks (KDIGO 2009). The use of direct acting HCV antivirals posttransplantation can also be considered and will likely be preferred in the future given improved tolerance and efficacy with these agents with an understanding that drug interactions with calcineurin inhibitors may occur. A study looking at 20 HCV-positive kidney transplant recipients (60% treated pre-transplant with interferon unsuccessfully) treated with direct acting antivirals posttransplant found that 100% cleared the virus and had a sustained virologic response at 12 weeks. The most common agents used were sofosbuvir and simeprevir (Sawinski et al. 2016).

Human Immunodeficiency Virus Infection

Human immunodeficiency virus (HIV) belongs to the family of Retroviridae. With the introduction of antiretroviral therapy (ART) in the mid-1990s, the incidence of HIV related deaths has been reduced. Renal diseases related to HIV infection include HIV associated nephropathy (HIVAN), immune complex diseases, and thrombotic microangiopathy (Frassetto et al. 2009). A total of 10% of patients with HIV develop HIVAN and it remains an important complication of HIV infection, progressing rapidly to end stage renal disease (ESRD) (Shahinian et al. 2000).

A large prospective clinical trial examining outcomes among 150 HIV⁺ kidney transplant recipients reported 3-year patient and graft survival rates of 88.2% and 73.7%, respectively, which were similar to survival rates among a cohort of unmatched elderly (>65 years) HIV-negative (HIV⁻) kidney recipients (Stock et al. 2010). The candidates for transplantation include those with well-controlled HIV infection with undetectable viral loads, CD4 >200 cells per microliter, and absence of untreatable infections or malignancies (Blumberg et al. 2009). The most significant complications in this patient population posttransplant include increased rejection rates (up to 25%), managing drug interactions between ART and immunosuppressive therapy and complications related to cardiovascular risk factors and hepatitis coinfection (Blumberg et al. 2009). The choice of ART should be based on susceptibility results and if possible, the use of protease inhibitors should be avoided owing to significant drug interactions with this class of ART. With regards to immunosuppressive therapy, the use of thymoglobulin may result in prolonged depression of CD4 counts, whereas monoclonal anti-IL2 receptor antibodies, such as basiliximab/daclizumab, have been shown to increase CD4 cell counts (Ciuffreda et al. 2007; Carter et al. 2006). The risks of antilymphocyte therapy should be balanced with the risks of rejection in HIV-infected recipients. Of note, HIV-positive donors can now be considered in HIV-positive recipients.

Respiratory Virus Infections

The various respiratory viruses that cause infection affecting the renal transplant patient population include adenovirus, respiratory syncytial virus (RSV), influenza, parainfluenza, human metapneumovirus, rhinovirus, and coronavirus (Green et al. 2004). Clinical manifestations include upper respiratory tract infection, bronchitis, and pneumonia. In addition to respiratory illness, adenovirus is known to cause gastroenteritis, hemorrhagic cystitis, pancreatitis, meningoencephalitis, necrotizing hepatitis, and nephritis/renal dysfunction in renal transplant recipients (Pham et al. 2003; Alsaad et al. 2007). Infection with these viruses may also be associated with rejection (Weikert and Blumberg 2008). Prevention involves hand hygiene and the use of droplet precautions for those suspected of having infection. Influenza vaccination is recommended prior to transplant and yearly following transplant. Treatment of respiratory viral infection involves supportive care and antiviral medications. Influenza can be treated with oseltamivir or zanamavir. Ribavirin is approved for the treatment of RSV. Adenovirus infection is treated with reduction of immunosuppression with consideration of cidofovir (Ison 2006).

Emerging Viral Infections

Emerging viral pathogens include newly recognized viruses or previously known viruses that are either increasing or threatening to increase in incidence. Some of the emerging viruses causing infections in renal transplant population include Human T-cell Leukemia Virus Type 1 (HTLV-1), Hepatitis E virus (HEV), Measles virus, Rabies virus, Lymphocytic Choriomeningitis virus (LCMV), Dengue virus (DENV), West Nile virus, and Zika virus. Case reports of adult T-cell leukemia (ATL) following renal transplantation in HTLV-1-positive patients have been documented, though in a case series of renal transplant recipients with long-term follow-up, no cases of ATL or HTLV-1-

associated myelopathy (HAM) developed (Nakamura et al. 2005; Tanabe et al. 1998). HEV may induce kidney injury with significant reduction in glomerular filtration rate. Glomerular injuries such as membranoproliferative glomerulonephritis have been described in kidney transplant patients with acute and chronic HEV infections (Kamar et al. 2012). The incidence of measles in transplant recipients is unclear. Cases of subacute measles encephalitis (SME) have developed in renal transplant recipients. The clinical course is one of deteriorating mental status and treatment refractory seizures (Waggoner and Deresinski 2013). Worldwide, vector-borne viral disease is increasing in incidence and can be transmitted with blood products and organ transplantation. Fatal cases of dengue have been reported within the first month following renal transplant (Waggoner and Deresinski 2013). West Nile virus has also been reported in transplant recipients with a high incidence of neuroinvasive disease and poor outcomes. Zika virus is also now a concern. Cases of donor-derived rabies in the SOT population have been reported. Patients typically developed encephalitis between 1 and 2 months posttransplant, and all symptomatic reported patients died (Srinivasan et al. 2005). Cases of LCMV causing severe disease in organ transplant patients have been documented. The 4 clusters of LCMV infection occurred in the United States and involved kidney, liver, and lung transplants; symptoms included fever, abdominal pain, nausea, diarrhea, and altered mental status (Srinivasan et al. 2005; Barry et al. 2008; Fischer et al. 2006). Two renal transplant recipients survived LCMV infection. Ribavirin has been employed in some cases, though the benefits remain unclear (Waggoner and Deresinski 2013). Data regarding the incidence, screening and treatment options of the above-mentioned emerging viruses are limited. Given the risk of donor-derived viral transmission, organs should not be accepted from donors with unexplained febrile or neurologic illness. In unclear cases, the risk of donor-derived infection should be balanced with the benefit of the transplant.

Bacterial Infections

Bacterial infections after renal transplantation can be due to surgical complications at the time of transplantation, nosocomial infection, immunosuppression, or community-acquired infection. Donor-derived bacterial infections from the transplanted kidney or blood stream can occur as well. About 47% of kidney transplant recipients develop bacterial infections (Patel and Paya 1997). Occurring any time posttransplantation, urinary tract infections account for the overwhelming majority of these infections and are the most common bacterial infections prolonging or leading to re-hospitalization (Wyner 1994). Enterococci, staphylococci, enteric gram-negative organisms, and *P. aeruginosa* are the most common bacteria isolated (Wyner 1994). Bacterial pneumonia, postoperative wound infections, and bacteremia or sepsis, although less common, also prolong or lead to re-hospitalizations after transplantation (Karuthu and Blumberg 2012). Common bacterial pathogens for these infections are gram-negative organisms, including multidrug resistant bacteria; gram positive organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant *enterococci* (VRE), as well as organisms more typically seen in immunocompromised patients such as *Listeria*. Months after the operation, bacterial pathogens include *Streptococcus* species, *Mycoplasma*, *Legionella*, *Listeria*, *Salmonella*, and *Nocardia*. Trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis has been shown to reduce the incidence of some of these infections. Increased antimicrobial resistance, urgency of treatment, drug interactions, and toxicities, as well as the risk for *Clostridium difficile* colitis all contribute to the complex decision making required for antimicrobial management.

Urinary Tract Infection (UTI)

Risk factors for urinary tract infection after transplantation are a prolonged period of hemodialysis before transplant, prolonged bladder catheterization, female sex, deceased donor transplant, kidney-pancreas transplant with bladder drainage,

uretero-vesical stents, and an increased immunosuppressed state (Karuthu and Blumberg 2012; Lapchik et al. 1992). Prophylaxis to lower the risk of infection after transplant with trimethoprim-sulfamethoxazole is routine (Karuthu and Blumberg 2012). Controversy regarding the exact dosing and duration of prophylaxis exists. Typically it is given at a dose of 160 mg trimethoprim and 800 mg of sulfamethoxazole daily for 6–12 months (KDIGO 2009). Trimethoprim-sulfamethoxazole reduces the risk of UTI and bacteremia (Karuthu and Blumberg 2012; Patel and Paya 1997).

Symptoms of UTI include frequency, urgency, and dysuria as well as nausea and vague abdominal complaints. Some patients are asymptomatic. *Escherichia coli* is the most common pathogen and an increasing number of pathogens are multidrug resistant. Sensitivity testing is required. Treatment of asymptomatic bacteriuria in the renal transplant recipient is controversial and is not routinely recommended (Coussement and Abramowicz 2013). Although not well studied, since UTIs in renal transplant patients are complicated, 7–14 days of antibiotics is a typical duration. Removal of stents and catheters as well as drainage of abscesses are frequently required to prevent relapse and for cure.

Surgical Wound Infections

Surgical wound infections, occurring at a rate of 3–4%, usually present within the first 4 weeks after transplant (Ramos et al. 2008). Obesity, urine leaks, re-operation through the original incision, diabetes, high creatinine levels in plasma, and prolonged bladder catheterization are risk factors for wound infections (Humar et al. 2001; Khoury and Brennan 2005). Improved organ procurement, preservation, and surgical techniques along with preoperative antibiotics all reduce the risk of subsequent postoperative wound infection. Bacterial organisms causing these types of infections may be nosocomial and multidrug-resistant making antibiotic treatment difficult due to limited options or toxicities. Source control with good wound care is critical in the management of these types of infections.

Bacterial Pneumonia

Although pneumonia is the most common bacterial infection in all solid organ transplant recipients, its incidence is lowest in those who have received a kidney (Khoury and Brennan 2005). Occurring early in the posttransplant period, CMV infection and rejection treatment with anti-lymphocyte preparations increase the pneumonia risk. Hospital-acquired pneumonia due to resistant pathogens, such as MRSA, and extended spectrum beta lactamase (ESBL) or carbapenem-resistant (CRE) gram-negative organisms are increasing in incidence and sometimes require nephrotoxic agents for treatment. Community-acquired pneumonia can occur any time after transplantation and the incidence of community-acquired pneumonia specifically due to *Streptococcus pneumoniae* can be lowered with vaccination.

Bacteremia

Bacteremia and sepsis are most commonly due to a urinary source, followed by lung, wound, and abdomen (Khoury and Brennan 2005). Intravenous catheters also play a role. Diabetes mellitus and posttransplant dialysis increase the incidence of sepsis which decreases the survival rate in these patients (Abbott et al. 2001). Prompt treatment with broad spectrum antibiotics followed by rapid de-escalation to pathogen-specific therapy based on sensitivities is required. Removal of foreign bodies such as intravenous catheters and stents is also necessary for cure.

Nocardia Species

Nocardia is a rare infection seen in the renal transplant recipient occurring in less than 4% of patients (Wilson et al. 1989). Trimethoprim-sulfamethoxazole prophylaxis used after transplant to prevent *pneumocystis jiroveci* pneumonia (PCP) likely prevents *Nocardia* infection as well. *Nocardia asteroides* is the most common species and causes pulmonary infections, including cavitory lesions

and pleural effusions (Patel and Paya 1997). Other common sites of infection, due to dissemination, are central nervous system (CNS) and cutaneous. All patients with *Nocardia* should be evaluated for CNS disease. Allograft rejection, high-dose prednisone, azathioprine, instead of cyclosporine based immunosuppression, and neutropenia are risk factors for this infection (Patel and Paya 1997). Diagnosis is made by the identification of branching and beading rods on gram and modified acid fast staining and cultures of infected sites. Antimicrobial susceptibility testing should be performed on all isolates. High dose trimethoprim-sulfamethoxazole sometimes in combination with amikacin is the treatment of choice, but allergic reactions and other side effects sometimes limit their use. Alternatives include imipenem, minocycline, and ceftriaxone, but choices should be based on susceptibilities and site of infection (Spelman 2016). *Nocardia* infections can relapse and prolonged therapy up to a year is recommended followed by chronic suppressive therapy (Spelman 2016; Arduino et al. 1993).

Listeria

Listeria monocytogenes is a bacterial organism that is transmitted most commonly during summer and early fall to humans via the gastrointestinal tract from contaminated dairy products, raw vegetables, and meat. Although more common during the first 2 months after transplantation, infection may occur at any point, and risk is increased with rejection therapy (Patel and Paya 1997). Infections involving the central nervous system, such as meningitis and meningoencephalitis, are most common and present with headaches, fever, meningismus, altered mental status, and possibly focal neurologic deficits including cranial nerve palsies and seizures (Patel and Paya 1997). Cerebrospinal fluid examination typically reveals a pleocytosis, mostly polymorphonuclear leukocytes, decreased glucose, and elevated protein, but as the name implies, a mononuclear predominance may occur instead. Gram staining has a low sensitivity and may be negative or reveal gram positive bacilli which may be

confused with diphtheroids. Other sites of infection include bacteremia, pneumonia, endophthalmitis, and septic arthritis. While trimethoprim-sulfamethoxazole, used for *P. carinii* prophylaxis, may also prevent infection with *Listeria*, the treatment of choice is intravenous ampicillin and gentamicin for up to 8 weeks in those with CNS infections to prevent relapses. Gentamicin is usually continued for a shorter duration, about 2 weeks if kidney function is stable. (Gelfand 2016). Trimethoprim-sulfamethoxazole is an alternative treatment for those who are allergic to penicillin. Decreasing immunosuppressive agents is sometimes, but not always necessary.

Legionella

Legionella infections in renal transplant recipients most commonly occur early in the post-transplantation period, but can be seen any time, especially during episodes of rejection. *Legionella pneumophila* is the most common species to infect humans, and although more commonly community-acquired, nosocomial transmission occurs (Patel and Paya 1997). Most infections are pulmonary including pneumonia, and abscess with cavitation. Symptoms are typical of lung infections but also may include headache and diarrhea. A legionella urinary antigen test and culture of lower respiratory secretions on selective media are used for diagnosis. Empiric treatment for Legionella is appropriate while waiting for results. Quinolone antibiotics, such as levofloxacin, are preferred over macrolides in renal transplant patients because of drug interactions between macrolides and immunosuppressive medications. Initially given intravenously, quinolone antibiotics can be quickly deescalated to oral treatment when the patient has defervesced. Renal transplant patients, especially those who are severely ill at presentation, should receive 21 days of treatment (Yu 2016). Along with PCP and *Listeria*, as noted above, prophylaxis with trimethoprim-sulfamethoxazole may also prevent Legionella infection.

Mycobacterium tuberculosis

Immunosuppression increases the risk of developing *Mycobacterium tuberculosis* (TB) disease. Although the majority of tuberculosis infections in renal transplant recipients occur in the first 18 months, TB can occur any time after transplantation (Khoury and Brennan 2005). Its overall incidence is lower in the United States when compared to the rest of the world, and foreign-born recipients are at greatest risk. Having a high index of suspicion is important in renal transplant patients because presentation can be atypical and pretransplant screening with tuberculin skin tests or IFN-gamma release assays are unreliable in chronic kidney disease patients due to anergy. Extra-pulmonary sites of infection and disseminated disease occur in about a third of cases (Karuthu and Blumberg 2012). Laryngeal, meningeal, skeletal, cutaneous, intestinal, and renal infections are examples of extra-pulmonary disease. Fevers are common, but sweats and weight loss may be absent (Patel and Paya 1997).

Screening prior to transplant should include a history regarding prior exposures, and treatment for TB, as well as a chest x-ray and urine AFB culture. Prophylaxis with isoniazid or rifampin should be offered to patients prior to transplantation with a history of inadequately treated TB, an abnormal chest x-ray suggestive of prior TB exposure, a positive PPD or IFN gamma assay, contact with someone with active TB, or a kidney from a PPD-positive donor in order to minimize reactivation disease after transplantation (Khoury and Brennan 2005). Patients receiving treatment for latent TB may undergo renal transplantation and complete their defined course afterwards with special attention to potential drug interactions and toxicities (Karuthu and Blumberg 2012).

Diagnosis of TB after renal transplantation often requires a biopsy of the infected site with stains for acid fast bacilli and cultures for sensitivity testing. Treatment of active disease after transplantation requires multiple drugs and should follow the American Thoracic Society, Center for Disease Control, and Infectious Disease Society of America Guidelines (MMWR 2003). Special attention to drug toxicities and interactions with

immunosuppressive agents is required. Rifampin, in particular, decreases cyclosporine levels and increases the risk for rejection.

Fungal Infections

Fungal infections in kidney transplant recipients occur less frequently than in other solid organ transplant recipients. Most present within the first 6 months after transplantation (Hagerty et al. 2003) and can represent primary, reactivated, or donor-derived infection. Those associated with geographic and environmental exposures include histoplasmosis, coccidioidomycosis, blastomycosis, and paracoccidioidomycosis. Others are considered opportunistic and include infections such as *Candida*, *Aspergillus*, and *Cryptococcus* (Karuthu and Blumberg 2012). Broad spectrum antibiotics, corticosteroids, diabetes mellitus, rejection therapy, CMV infection, and duration of pre-transplant dialysis are risk factors (Khoury and Brennan 2005). Esophageal candidiasis, urogenital candidiasis, and pneumonia are the three most common sites of fungal infections in these patients (Abbott et al. 2001). Clinical presentation may be nonspecific and diagnosis difficult due to testing limitations. Positive cultures may represent colonization rather than infection with pathogens such as *Candida* and *Aspergillus*. Cultures, antigen assays, serum galactomannan assays, and radiography may be helpful, but are not always diagnostic. Subsequently, biopsy with pathology and cultures is considered the gold standard for diagnosing fungal infections (Karuthu and Blumberg 2012). Drug interactions and toxicities as well as immune reconstitution, due to lowering of immunosuppressive medications, further complicate the management of fungal disease in these patients and require expert advice (Karuthu and Blumberg 2012).

Pneumocystis jiroveci

Pneumocystis jiroveci (formerly *Pneumocystis carinii* (PCP), protozoa) is a pathogen currently

considered a fungus based on nucleic acid and biochemical analysis. Presenting as pneumonia with interstitial infiltrates on chest x-ray within the first year after transplantation in those not receiving prophylaxis, mortality may be high. Nonproductive cough and shortness of breath with rapid progression to hypoxia is a classic presentation. Diagnosis is based on silver staining of deep respiratory specimens from induced sputum, bronchoalveolar lavage, or transbronchial biopsy (Martin and Fishman 2013). The treatment of choice is high dose trimethoprim-sulfamethoxazole for 21 days with corticosteroids in hypoxic patients (partial pressure of oxygen of <70 mmHg on room air) tapered over 14 days. Atovaquone or clindamycin plus pyrimethamine are alternative agents (Martin and Fishman 2013). Trimethoprim-sulfamethoxazole prophylaxis for 6–12 months after transplantation is highly effective in preventing this infection and should be administered to all renal transplant patients if tolerated. Frequently used alternatives for prophylaxis in allergic patients include dapsone (if glucose-6 phosphate dehydrogenase levels are normal) and atovaquone.

Conclusion

Infection remains an important concern in patients undergoing kidney transplantation. Attention to pretransplant screening of the potential organ donor and recipient is essential to optimizing transplant outcomes. Advances in the management of transplant-related infections include the increasing use of rapid molecular diagnostic testing as well as improvements in the approach to prophylaxis and treatment. Ongoing challenges include the need for prolonged immunosuppression to prevent organ rejection, drug-drug interactions, and the management of resistant and emerging pathogens. Continued awareness of the risks, timing, and presentation of infection posttransplant and strategies to reduce its impact will contribute further to progress in the field of kidney transplantation.

Cross-References

- ▶ Donor Selection: Deceased Donor
- ▶ Ethical Issues in Organ Transplantation
- ▶ Living Donor Evaluation and Selection
- ▶ Necessary Components of a Living Donor Team
- ▶ Recipient Selection for Kidney Transplantation
- ▶ Transplant Immunosuppression

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