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Infections in Kidney Transplant Recipients

Deepali Kumar and Atul Humar

Kidney transplantation is the most common type of transplant performed worldwide. Since 1988, more than 370,000 kidney transplants have been performed in the United States [1]. Kidney transplantation has been shown not only to benefit a patient's quality of life but is also more cost effective than dialysis. Transplantation can be performed using deceased or living donor kidneys. The native kidneys are generally left in situ and the transplant kidney is grafted in the right lower abdominal quadrant. The transplant procedure generally consists of anastomoses of the renal artery and vein to the native external iliac artery and vein, respectively. The donor ureter is anastomosed to the recipient bladder.

Posttransplant infections in renal transplant recipients occur in 44.9–81 % patients and include urinary tract infections (UTIs), bacteremia, pneumonia, wound infection, and cytomegalovirus (CMV) infection [2–6]. Severe sepsis posttransplant often causes graft dysfunction [7]. Although there is no specific classification of infections post kidney transplant, these generally follow the timeline of infections post solid organ transplant described previously by Fishman and Rubin [6, 8], with some caveats specific to renal transplantation. The specific infections unique in some aspect to kidney transplantation will be the focus of this chapter. Other infections that are common to all transplant patients are discussed briefly and serve to provide a contextual basis for understanding the global infectious disease burden in kidney transplant recipients.

Postoperative complications and early UTIs are seen in the first month posttransplant. Donor-derived infection should also be considered early in the posttransplant period. During months 1–6, opportunistic infections such as reactivation of herpesviruses, BK virus, and fungal and mycobacterial infections are seen. However, it is important to note that with ongoing prophylaxis and the use of potent antirejection therapies, the initial onset of some infections such as >*Pneumocystis jirovecii* and cytomegalovirus reactivation can occur after 6 months.

12.1 Pretransplant Evaluation of the Kidney Recipient

The pretransplant evaluation of the kidney transplant patient includes obtaining a history of infectious diseases, infectious exposures, and immunizations [9]. Generally, active infectious diseases should be resolved and/or adequately treated prior to undergoing kidney transplant. During the evaluation for transplant, serologic screening for human immunodeficiency virus (HIV), hepatitis C virus (HCV), hepatitis B virus (HBV), human T-cell lymphotropic virus (HTLV), CMV, EBV, herpes simplex virus (HSV), Varicella-Zoster virus (VZV), and syphilis is done and each result needs to be carefully evaluated. HIV is no longer a contraindication to kidney transplant and is discussed further in section Kidney Transplantation in the HIV-Positive Recipient [10]. The knowledge of CMV and Epstein–Barr virus (EBV) serologic status is important to guide antiviral prophylaxis posttransplant. Hepatitis C antibody and hepatitis B surface antigen positivity are not contraindications to renal transplant but the extent of liver disease should generally be delineated with pretransplant liver biopsy. If possible, attempts to treat these viruses should be made prior to transplant. Studies indicate that treatment of HCV with interferon-α and ribavirin posttransplant leads to a 60–70 % rate of allograft rejection [11, 12]. However, this is not an issue with the new protease inhibitors for HCV [13]. On the other hand, hepatitis C-positive recipients could be considered for a kidney transplant from a hepatitis C-positive donor.

Persons who are HTLV-I or -II positive should be assessed on an individual basis. In endemic areas, there is a risk of progression of 2–4 % to HTLV-I-associated myelopathy/tropical spastic paraparesis [14]. A positive syphilis screening test should lead to a confirmatory test specific for syphilis antigens. If a confirmatory test is positive, the patient should be treated prior to transplant. Tuberculosis (TB) skin testing should be routinely performed although a positive skin test is not a contraindication to transplant. False negative skin tests

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can occur in hemodialysis patients [15–18]. Interferon-γ release assays (IGRAs) for TB may also be used for screening in this population. These include the QuantiFERON-TB Gold and T.Spot.TB, both of which measure the amount of interferon-γ released in response to ex vivo cell stimulation with TB-specific antigens. Recent studies have shown that these assays may have improved test characteristics in the hemodialysis population when compared to the tuberculin skin test (TST) [15, 16]. Patients found to have latent TB can be initiated on therapy prior to transplant and complete the course posttransplant if necessary. This consists of isoniazid 5 mg/kg once daily or 900 mg thrice a week (plus vitamin B6) for 9 months [18]. A shorter 4-month course of rifampin may also be effective; however, rifampin will have significant drug interactions with immunosuppressives if transplant occurs while on treatment. An immunization record should also be obtained to ensure routine vaccinations are up to date [19]. Pretransplant, patients should have received tetanus toxoid and pneumococcal vaccine. Immunity to varicella, measles, mumps, and rubella should be determined. If immunity is absent, then varicella and MMR vaccines should be given; however, since these are live vaccines, the transplant should be on hold for 4 weeks after vaccine is given. Hepatitis A and hepatitis B vaccines should also be updated prior to transplant.

12.2 Donor Screening and Donor-Derived Infections

There are some important considerations with regard to donor infections and transmission in the context of kidney transplantation, which may be unique compared to other organs. First, since an alternative exists to kidney transplantation, that is, dialysis, the willingness of physicians or patients to undertake potential risks of infectious diseases transmission associated with certain types of donors may be different than those for other organs. For example, the risk benefit consideration for a critically ill patient with heart failure may be very different than a patient on dialysis. Second, since for deceased donors, usually two kidneys are transplanted, the opportunity exists for early diagnosis of a donor-derived infection that may be transmitted through the allograft, since both recipients may become ill at similar times.

Deceased kidney donors require appropriate screening for infectious diseases [9]. A history should elicit cause of death as well as previous infectious exposures including those potentially acquired during previous travel such as malaria, TB, and rabies. Donor screening generally includes serologic studies for HIV, HCV, HBV (surface antigen and total core antibody), CMV, EBV, and syphilis (discussed in detail in Chap. 7). Additional screening may include West Nile virus (WNV) nucleic acid testing (NAT), which may be dependent on local WNV activity, and the particular policies of the organ procurement organization. HTLV I and II screening is also done in some jurisdictions. Deceased donors should also undergo screening blood and urine cultures. Donors with a history of high-risk behavior may undergo additional testing (NAT) to determine whether they are in the "window period" of seroconversion for HIV, HBV, or HCV. For some OPOs it may be routine to offer NAT testing for all donors. Controversy exists whether organs from increased risk donors should be used for kidney transplantation or not. However, based on a decision analysis, utilization of high risk organs is beneficial even in kidney transplant recipients [20]. A standardized informed consent may increase patient acceptability of these organs [21]. Organs from HCV-positive donors may be considered for use in HCV-positive kidney transplant recipients. Alternatively, the situation may arise where a donor may have previously been treated for HCV and achieved sustained virologic response. In this case, it is controversial whether the kidney should be transplanted in a HCV-negative recipient, since the risk of transmission is largely unknown [22]. Recent consensus guidelines indicate that individual consideration should be given to use of isolated hepatitis B core antibody-positive donors with antiviral prophylaxis in the recipient as the risk of active hepatitis B is low [23]. It is impractical to screen donors for TB using TST; deceased donor screening with Quantiferon-TB in the research setting results in a high number of indeterminate tests [24]. Bacteremic donors are generally acceptable with antibiotic treatment of the recipient [25]. However, caution should be used when donors are bacteremic with multidrug-resistant organisms.

Unusual pathogens such as rabies and lymphocytic choriomeningitis virus (LCMV)/arenavirus have been transmitted to renal transplant recipients, although these cases are rare and difficult to predict [26–31]. There have been no LCMV seroprevalence studies in donors and it is unknown whether donors with rodents are at greater risk. To avoid transmission of unusual viruses, we recommend not to use organs from donors who had died of an unknown form of meningitis or encephalitis. Other pathogens that have been transmitted via donors to kidney transplant recipients include malaria and syphilis [32–35]. These are generally treated successfully if they are recognized early. Unusual fevers or illnesses posttransplant, especially in the first month posttransplant, are alerts for donor-derived infections. In these cases, it is important to revisit the original donor evaluation as well as to investigate whether recipients of other organs from the same donor are experiencing similar illness.

Living kidney donors also undergo screening similar to that of cadaveric donors. However, living donors should also be screened for latent TB using a TST. If determined to have latent TB infection, the donor should ideally complete therapy for latent TB prior to donation [36]. As an alternative, the recipient can be treated with isoniazid for 9 months posttransplant. In the latter case, treatment should be initiated as soon as possible posttransplant since the greatest risk of TB

reactivation is in the first year [37]. *Strongyloides* sp. antibody testing and screening for *Trypanosoma cruzi* (the agent of Chagas disease) should also be done in living donors from endemic areas [38].

12.3 Technical Complications Leading to Infection

Technical problems after kidney transplantation can arise due to either vascular or nonvascular complications. Infections related to these complications usually, but not always, present in the early postoperative period. Overall, the risk of such complications is generally lower than that of other types of transplants. Surgical wound complications are probably the most common and include wound infection, dehiscence, incisional hernias, and lymphoceles [39, 40]. Ureteral complications include urinary leaks and ureteral strictures. Other postoperative issues include vascular thrombosis or bleeding and hematoma formation. In one retrospective study of 870 patients who underwent deceased donor kidney transplant, at least one surgical complication occurred in 34 % [40]. Wound complications occurred in 10.5 % with isolated lymphoceles in 6 %. Risk factors for wound complications include obesity, older age of donor and recipients, as well as certain immunosuppressive drugs such as mycophenolate mofetil (MMF) and sirolimus [40, 41]. The incidence of posttransplant lymphocele is 0.6–18 %, the majority of which are small and asymptomatic [42]. However, approximately 6 % can be infected [43]. Generally, asymptomatic lymphoceles can be followed by ultrasound although clinical symptoms or unresolving lymphoceles should lead to further investigation with percutaneous aspiration and culture. Urinary leaks usually occur at the anastomosis (at the site of vesicoureteral junction) and may occur due to ischemia of the ureter, and can lead to the formation of a urinoma. Although uncommon, urinomas occasionally become infected primarily with Enterobacteriaceae, although other organisms may be seen [44]. Strictures also occur primarily at the anastomosis of the ureter to the bladder, and may be secondary to ischemia or rarely due to BK virus, and lead to recurrent graft pyelonephritis.

12.4 Urinary Tract Infections

By far, the most common infection in a renal transplant recipient occurs in the urinary tract. Incidence has been estimated to be 4–86 % in some series [45–47]. Risk factors for UTI can be divided into pretransplant, intraoperative, and posttransplant factors. Pretransplant factors include female sex, diabetes mellitus, pretransplant immunosuppression, urinary tract abnormality, and dialysis [45, 48]. Intraoperative factors include use of a JJ stent, prolonged catheterization, infected organ, and retransplantation. Routine ureteric stenting during transplant has been shown to decrease the risk of urologic complications but results in a 1.5 times increase in relative risk of UTI [49]. Postoperatively, the risk of UTI is increased if graft dysfunction is present. UTIs can occur at any time posttransplant and timing may in part be dependent on the use of prophylaxis. Symptomatic patients with cystitis may have dysuria, hematuria, frequency, urgency, suprapubic pain, or foul urinary odor. A urinalysis generally shows pyuria and a urine culture reveals significant bacterial growth. Significant growth in the nontransplant literature is generally defined as $>10^5$ colony forming units/mL of urine (or $>10^8$ cfu/L) of a single organism. Significant pyuria is defined as >10 WBCs per hpf. However, lower bacterial colony counts, and limited detection of pyuria, may also occur in renal transplant recipients with significant infection. Acute allograft pyelonephritis is diagnosed if in addition to the abovementioned clinical picture, fever or tenderness over the allograft is present. Bacteremia and a decline in renal function may also be the features of acute pyelonephritis. Atypical presentations are common, and include isolated febrile syndromes, isolated graft tenderness, and other presentations. Emphysematous pyelonephritis is a rare entity that can occur in kidney transplant recipients and often requires transplant nephrectomy in addition to antimicrobials [50, 51]. However, conservative management with antimicrobials and percutaneous nephrostomy has also been reported [52].

Antimicrobial therapy for simple UTIs or graft pyelonephritis should be directed at the organism recovered in urine culture. The duration of therapy for UTI in renal transplant recipients has not been well studied. Graft pyelonephritis can usually be treated with a 2- to 3-week course of appropriate antibiotic therapy. However, longer durations of antimicrobial therapy can generally be used for severe allograft pyelonephritis, recurrent UTIs, and those with structural abnormalities, such as ureteric stents, ureteric strictures, and stones.

Several studies have examined the consequences of UTI in the kidney transplant population. In the first 6 months, UTI appears to be associated with bacteremia and acute rejection [53]; UTI occurring after 6 months (termed late-onset UTI) is shown to be associated with death and graft loss in a large retrospective study [54]. Several mechanisms are postulated for impaired graft function including production of inflammatory cytokines and free radicals or associated acute rejection [45, 55]. Studies have shown that acute graft pyelonephritis can have a deleterious effect on long-term allograft function [56–59]. Giral et al. [57] reviewed 1387 renal transplant recipients, of which 13 % developed allograft pyelonephritis during the follow-up. Pyelonephritis within the first 3 months was significantly associated with poorer graft outcome. Microbial virulence factors have also been associated with acute allograft injury. In one study characterizing *Escherichia coli* isolates from kidney transplant recipients with UTI, the expression of P fimbriae in these isolates was significantly associated with acute allograft injury [60].

To prevent early UTIs, antibacterial prophylaxis with trimethoprim-sulfamethoxazole (TMP/SMX) up to 1 year posttransplant has been advocated by some investigators [61–63]. A small randomized trial of low-dose versus high-dose TMP/SMX showed a significant decrease in UTI occurrence in the high-dose TMP/SMX group (49.2 % versus 25 % patients, $P<0.05$). This suggests that doses used for *Pneumocystis* sp. prophylaxis do not necessarily prevent UTI. This approach is also limited by rising antimicrobial resistance to TMP/SMX. In one single-center review of UTIs in 161 kidney transplant recipients, 25 % of patients developed UTI despite receiving TMP/SMX prophylaxis [64]. Ciprofloxacin is also shown to be effective although quinolone prophylaxis would not prevent pneumocystis infections [65]. In a retrospective review comparing kidney transplant patients that received TMP/SMX versus ciprofloxacin prophylaxis, the latter group was found to have significantly less UTIs at 1 year posttransplant [66]. However, rising rates of fluoroquinolone resistance in solid organ transplant recipients were found in a study of gram-negative bacteremia and may also limit their use [4]. The increasing prevalence of multidrug-resistant organisms including carbapenem-resistant enterobacteriaceae is a major concern in many centers [67, 68]. In small case series, fosfomycin has been used safely to treat drug-resistant infections [69].

12.5 Asymptomatic Bacteriuria

Many kidney transplant programs will do routine urinalysis and culture frequently in the initial postoperative period and continue to monitor at regular intervals thereafter. There is no clear consensus on whether to monitor and if done then how often to monitor the UTI [70]. In many cases, a urine culture may be obtained routinely at the time bloodwork is drawn regardless of patient symptoms. It is unclear how many cases of asymptomatic bacteriuria progress to symptomatic infections or allograft pyelonephritis. However, many physicians will err on the side of treatment especially in the early posttransplant period [48]. Although there is little evidence to support this approach, early in the postoperative period, multiple factors may be present, such as induction immunosuppression, indwelling urinary catheters, urinary stents, and delayed graft function. One small study found that asymptomatic bacteriuria early posttransplant may be a risk factor for symptomatic UTIs—although not with the same organism [71]; others have found no benefit of treating asymptomatic bacteriuria [72]. Ultimately, although there is no clear consensus whether asymptomatic bacteriuria should be treated, there is evidence to suggest that subclinical UTIs may cause allograft damage. One study has shown increased levels of urinary inflammatory cytokines in patients with asymptomatic bacteriuria versus controls [55]. Dupont et al. [73] showed that allograft scarring could occur with asymptomatic bacteriuria even in the absence of vesicoureteral reflux and suggested prophylaxis for asymptomatic infection. Another situation where asymptomatic bacteriuria should be treated is in pregnant transplant recipients.

12.6 Recurrent Urinary Tract Infections

Recurrent UTIs in a renal transplant recipient is defined as ≥3 UTIs per year. Predisposing factors that should be ruled out include vesicoureteral reflux, neurogenic bladder, structural abnormality such as the presence of a ureteric stricture or calculi, or chronic bacterial prostatitis. A persistent renal or perirenal abscess could also serve as a focus of infection for recurrences. Patients with underlying polycystic kidney disease may have cyst infection of the native kidney. Ideally, abdominal imaging with a CT scan or ultrasound should be done to evaluate the transplanted and native kidneys. Referral to a urologist for cystoscopy may be necessary to rule out other structural abnormalities. In many cases, no correctable abnormality is found. If relapse occurs after a 2-week course of antibiotics, then a 4- to 6-week course of antibiotics can be attempted. In a few cases, patients will require long-term antibiotic prophylaxis. The goal is to suppress bacteriuria and one potential approach is to obtain routine cultures while on prophylaxis to see if bacteriuria is suppressed. If prophylaxis is instituted, patients should be reevaluated at regular intervals (e.g., every 6 months) to determine the need for ongoing therapy. If bacteriuria persists or a relapse occurs while on prophylaxis, then this strategy needs to be re-evaluated. Prophylaxis options include amoxicillin, fluoroquinolones, oral cephalosporins, TMP/SMX, and nitrofurantoin. Susceptibilities from the last urinary isolate can be used to guide prophylaxis. A major limitation of prophylaxis is the selection of drug-resistant organism, a common problem in these patients. One study showed that infection by a multidrug-resistant bacteria significantly increased the risk of recurrent UTIs [74]. A reduction in immunosuppression, if possible, and optimal control of other variables such as diabetes mellitus may also help. A summary of microbial etiology and management of various forms of urinary infection is provided in Table 12-1.

12.7 Candiduria

Candiduria is defined as the presence of $>10^5$ Candida organisms in mid-stream urine. There is no clear consensus on whether all candiduria in the kidney transplant setting should be treated. Safdar et al. [75] reviewed the epidemiology of candiduria in 192 renal transplant recipients. Predictors of candiduria in this population were similar to those in the general population and included female sex, intensive care unit admission, antibiotic use, and diabetes. Candiduria was

TABLE 12-1. Suggested management of various clinical presentations of urinary tract infection in renal transplant recipients

Clinical presentation	Microbial etiology	Suggested management
Symptomatic cystitis	Enterobacteriaceae, *Enterococcus* sp., staphylococci, *Pseudomonas* sp., *Candida* sp.	Empiric oral therapy: first line: ciprofloxacin 500 mg PO b.i.d. ± amoxicillin 500 mg PO tid. Then directed therapy once culture results available. Treatment duration 5–7 days
Allograft pyelonephritis	As above, if culture is negative, consider unusual causes—e.g., adenovirus, mycoplasma (see "Sterile pyuria" row below)	Empiric therapy with IV or oral antibiotics as above. Directed therapy once culture results are available. Treatment duration 2–4 weeks
Recurrent UTI	As above	Rule out structural causes or persistent focus of infection. Consider oral antibiotic prophylaxis and re-evaluate in 6 months
Asymptomatic bacteriuria	As above	No need for empiric therapy. Await culture and susceptibility for directed therapy. Repeat culture to rule out contamination. Treat if stent is present or within 6 months posttransplant or persistent bacteriuria with same organism
Sterile pyuria	*Mycobacterium* sp., *Chlamydia trachomatis, Ureaplasma urealyticum*, fungi	Urine culture for acid-fast bacilli, fungi, other special testing as indicated
Yeast	*Candida* sp., unusual causes—*Malassezia* sp., *Trichosporon* sp.	Remove risk factors (urinary catheter, broad-spectrum antibiotics), rule out fungal bezoar by imaging, repeat urine culture, if symptomatic or persistent funguria, treat with fluconazole 400 mg daily. If fails to eradicate, then speciate and do susceptibility testing. Avoid amphotericin products

associated with decreased survival, likely reflecting severity of illness; however, therapy of asymptomatic candiduria was not associated with increased survival. On the other hand, candiduria may be a marker of fungal aggregates along the urinary tract, which can cause obstruction [76–78]. An attempt should be made to reduce risk factors such as removal of urinary catheters or avoidance of broad-spectrum antibiotic therapy. Fluconazole can be used as empiric therapy although persistent candiduria should lead to abdominal imaging to rule out a persisting source and removal of urinary catheter if present. If funguria persists, the yeast should be speciated and undergo susceptibility testing. If the isolate is found to be fluconazole resistant, therapy can be escalated to expanded spectrum azoles or echinocandins depending on susceptibility patterns.

12.8 Graft-Site Candidiasis

In a large review of 18,617 kidney transplants, the incidence of graft-site candidiasis was 1 per 1000 [79]. The majority of these infections have occurred in the first 3 months posttransplant. Many of these infections involved a fungal arte rial aneurysm. Usually, these are secondary to a single *Candida* sp. (primarily *C. albicans*) although bacterial coinfection has been found. Over 20 cases of fungal arterial aneurysm have been described in the literature from 1972 to 2015 [80–82]. In several, but not all, cases, *Candida* sp. was also recovered from organ preservation fluid. The significance of recovering *Candida* sp. from graft preservation fluid is unclear. Matignon et al. [83] have shown that of eight kidneys transplanted where preservation fluid was infected with *Candida* sp., none developed arterial aneurysm after 1–2 years of follow-up. Albano et al. [79] reviewed the cases of graft-site candidiasis in renal transplant centers in France from 1997 to 2005. Of the 18 cases found, 13 were due to *C. albicans* and others due to other *Candida* sp. Although most cases were that of fungal arteritis, infected urinoma, graft-site abscess, and surgical site infection also occurred. Treatment of fungal arteritis consists of antifungals and surgical ligation of the external iliac artery. Transplant nephrectomy is required in 50–70 % of cases and death has occurred in 17–50 % of cases especially where diagnosis is delayed. This is a serious complication of transplantation and important to recognize since massive bleeding can quickly lead to death.

12.9 Cytomegalovirus

CMV remains one of the most common opportunistic infections post kidney transplantation. While CMV is discussed in detail in Chap. 23, there are several important aspects unique to kidney transplantation. CMV reactivates in up to 50 % of renal transplant recipients depending on other risk factors such as donor/recipient serostatus, use of prophylaxis, and type of immunosuppression [84, 85]. In the current era, reactivation of CMV after renal transplantation most commonly presents as detection of asymptomatic viremia. In patients who present with symptoms, the majority has a flu-like illness with one or more of fever, malaise, and myalgias termed "CMV syndrome." CMV may also cause end-organ disease including enteritis, hepatitis, and pneumonitis, and rarely allograft nephritis. CMV has also been shown to have "indirect" or "immunomodulatory" effects in the transplant population. In the renal transplant setting, CMV has been associated with acute kidney rejection although the association of CMV with chronic allograft dysfunction is less certain [86–89]. A study comparing CMV prophylaxis

versus preemptive therapy demonstrated improvement in long-term graft survival with the use of prophylaxis [90].

The greatest risk of reactivation is in patients who are seronegative but receive an organ from a seropositive donor (D+/R−). For this group, universal prophylaxis with antivirals for 3–6 months posttransplant has been suggested [85]. The majority of large randomized controlled trials have either had a majority of kidney recipients or included only kidney recipients. In many instances, these results have been extrapolated to other transplant populations. The IMPACT trial compared 3 months with 6 months of valganciclovir prophylaxis in 319 D+/R− kidney transplant recipients. The incidence of CMV disease in the two arms was 36.8 % versus 16.1 %, respectively [91]. Longer term follow-up of these patients did not reveal an increased incidence of late onset CMV disease beyond the first year posttransplant in the group that received 6 months prophylaxis [92]. Routine viral load monitoring for CMV after the prophylaxis period is employed by some centers although its utility is unknown [93, 94]. Other tools such as cell-mediated immunity assessment may be of better utility for predicting late-onset CMV disease [95]. Various regimens are available for prophylaxis and include oral valganciclovir, oral ganciclovir, and valacyclovir [96, 97]. However oral ganciclovir is no longer available in many jurisdictions. Valacyclovir prophylaxis has only been extensively studied in the renal transplant population and appears to be effective [98]. Use of valacyclovir in D+/R− patients was also associated with a significant reduction in acute rejection episodes [98] but this finding has not been replicated in more recent studies [91]. Recipients that are seropositive are also at risk especially when antithymocyte globulin preparations are used for induction immunosuppressive therapy. These patients are either given antiviral prophylaxis for the first 3–6 months posttransplant or monitored at regular intervals with molecular assays (pre-emptive therapy) [85].

Treatment of CMV consists of induction doses of intravenous ganciclovir 5 mg/kg b.i.d. or oral valganciclovir 900 mg b.i.d. until viremia is at a low or undetectable level. Thereafter, maintenance doses can be used. In a randomized, multicenter study of intravenous ganciclovir versus oral valganciclovir for CMV disease, success rates were not significantly different, and current recommendations suggest that oral therapy can be used first line for mild to moderate CMV disease [84, 99]. It is worth noting that the majority of patients included in randomized treatment study were renal transplant recipients. In addition, long-term clinical or virologic recurrences were not significantly different between groups [100].

12.10 Polyomavirus

Polyomavirus-associated nephropathy (PVAN) is an important cause of graft dysfunction and graft failure. The incidence of PVAN ranges from 1 to 10 %; the majority of infections are due to BK virus-associated nephropathy (BKVAN) and very rarely PVAN may be due to JC virus alone [101]. In the modern immunosuppressive era, BK virus is one of the most important causes of infections after kidney transplantation and is discussed fully in Chap. 30. The pathogenesis, epidemiology, and management are briefly described in the following text.

After primary infection, the virus establishes latency primarily in the urogenital tract including renal cortex, medulla, urothelial cells, and bladder. The majority of viral reactivation occurs in the first year posttransplant. Reactivation of polyomavirus in the ureter can lead to stenosis whereas bladder reactivation can manifest as hemorrhagic cystitis. However, both of these are uncommon complications after kidney transplantation. Reactivation, replication, and inflammation within the kidney result in BKVAN. Usually, the only clinical manifestation is a rise in serum creatinine. A definitive diagnosis of BKVAN is made by kidney biopsy that demonstrates varying degrees of inflammation and/or fibrosis, often with intranuclear viral inclusions. Immunohistochemical staining using antibody directed against the SV40 T antigen or VP capsid proteins shows a characteristic nuclear staining reaction. Since disease may be patchy, a biopsy may occasionally be false negative.

Various risk factors for BKVAN have been suggested in several studies [102–106]. These include human leukocyte antigen (HLA) mismatches, history of acute rejection and use of antilymphocyte therapy, recipient age > 55, and recipient seronegativity. However, a large study of 1001 renal transplant recipients, 4 % of whom developed BKVAN, did not find any specific risk factors [107]. Recently, the use of more aggressive immunosuppression protocols such as with ABO incompatible transplants have been associated with a higher risk for BKVAN [108]. In another study, BK viremia was associated with the use of tacrolimus-mycophenolic acid combination versus cyclosporine-based immunosuppression [109].

The cornerstone of therapy for BKVAN is reduction in immunosuppression. All other options are less well studied and randomized controlled trials are lacking. Cidofovir, which is a nucleotide analogue of cytosine, has activity against DNA viruses. Results of case reports and series with cidofovir are difficult to interpret due to the concomitant decrease in immunosuppression [110]. Brincidofovir is a lipid conjugated oral formulation with decreased toxicity and appears to have activity against BK virus [111]. Further studies are ongoing. Leflunomide also appears to have antiviral properties in addition to its immunosuppressive action. Josephson et al. [112] showed stabilization of renal function in the majority of patients with BKVAN treated with leflunomide [112]. However, in a study of 52 patients treated with leflunomide, there was no association with viremia clearance and no correlation between serum concentrations of its metabolite A77 1726 and clearance [113]. Although leflunomide has been used as a treatment option, its adverse effects include hemolysis, transaminitis, and pancytopenia. Other experimental therapies that have been attempted or proposed

include fluoroquinolones, intravenous immunoglobulin (IVIg), and rituximab [114]. However in a recent randomized trial of 3 months of levofloxacin versus placebo for prevention of BK viruria and viremia, no benefit was demonstrated [115]. In addition, in a placebo controlled trial for treatment of BK viremia, in 39 patients, no beneficial effort of levofloxacin was observed [116]. Finally, the risk of recurrence after retransplantation for graft loss secondary to BKVAN does not appear to be increased [117].

It is well established that BK viruria and viremia are a prerequisite for histologically proven BKVAN. Given the lack of specific treatment for BKVAN and the high incidence of graft loss, routine screening for BK virus for early detection in the first year posttransplant is now recommended by most authorities [118]. Screening may be done by NAT testing of urine or plasma/blood. Detection of virus in the urine in itself has poor predictive value for BKVAN, but should trigger testing in blood or plasma. Detection of viremia is a better predictor of BKVAN and early intervention with judicious lowering of immunosuppression prevents the development of BKVAN.

12.11 Other Viral Infections Post Kidney Transplant

12.11.1 Adenovirus

Adenoviruses are non-enveloped DNA viruses with at least 52 known serotypes that are capable of causing a variety of illness in immunocompetent and immunocompromised hosts [119]. This includes upper and lower respiratory tract infection, conjunctivitis, keratoconjunctivitis and pharyngoconjunctival fever, hepatitis, and disseminated disease. Although adenovirus disease may manifest with these clinical syndromes in kidney transplant patients, several cases of adenovirus-related disseminated disease, pyelonephritis and hemorrhagic cystitis have also been described [120, 121]. Hofland et al. [122] reviewed 37 cases of adenovirus hemorrhagic cystitis in kidney transplant patients. All cases occurred within the first year posttransplant and the majority presented with fever and dysuria and hematuria. Graft dysfunction was present in the majority of patients and viral changes or acute rejection may be seen in kidney biopsies. Adenovirus species B predominates with serotypes 7, 11, 34, 35 causing most of the diseases. Diagnosis can be made by indirect methods such as serology or methods that directly demonstrate the presence of virus such as plasma polymerase chain reaction (PCR) and culture. In situ hybridization, immunohistochemistry, or PCR of fixed tissue can also identify adenovirus. Routine monitoring for adenovirus is not beneficial. In a surveillance study using blood PCR for adenovirus, it was found that self-limited adenoviremia can occur in 7 % of solid organ transplant patients with 58 % being asymptomatic [123]. There is no specific therapy for adenovirus, although clinical studies have focused on cidofovir and ribavirin. As discussed above, brincidofovir is a new oral lipid-conjugated cidofovir that has in vitro activity against many DNA viruses including adenovirus, and may be an option in the future. Immune reconstitution plays an important role in the clearance of adenovirus; therefore, decreasing doses of immunosuppressive medication is important.

12.11.2 Parvovirus B19

Parvovirus is a single-stranded DNA virus of the genus *Erythrovirus*. Although most infections are nonspecific flu-like illnesses, specific clinical syndromes have been described. In children, parvovirus infection is termed “fifth disease” that causes a facial rash resembling “slapped cheeks”; adults with parvovirus can develop a polyarthropathy syndrome; the virus can also lead to transient aplastic crisis in those with chronic hemolytic anemia and hydrops fetalis leading to intrauterine fetal death in pregnant women. Infection in transplant recipients is unlike that of immunocompetent patients in that viral replication can persist for prolonged periods of time [124]. Recurrent parvovirus infections have also been described [125]. Onset of parvovirus-associated syndromes can occur at any time posttransplant and has been described as early as 2 weeks. One study of 60 adult kidney transplant patients showed a 10 % rate of parvovirus viremia in the first year posttransplant [126]. The mode of acquisition of the virus is unknown in renal transplant recipients. Possibilities include inhalation of infected aerosols as in the immunocompetent host but also transmission from the donor. The possibility of viral reactivation also exists such as in the case of herpesviruses although little is known about parvovirus latency or cellular reservoirs. Parvovirus has well-established association with hematologic abnormalities including pure red cell aplasia and acute or chronic anemia in kidney transplant recipients. Since anemia is such a common problem in renal transplant recipients, it is important that physicians keep this diagnosis in mind especially for cases of severe, unexplained, or recalcitrant anemia. In one series, 3 out of 8 (38 %) of renal transplant patients with erythropoietin-resistant anemia (Hgb < 10 g/dL) were parvovirus positive by qualitative plasma PCR [127]. Other cell lineages may also be affected and lead to leucopenia and thrombocytopenia. Less well-developed associations exist with transient allograft dysfunction, collapsing glomerulopathy, acute rejection, and thrombotic microangiopathy. Other associations in renal transplant recipients have also been described such as hepatitis, encephalitis, and cerebral angiitis. Serologic studies have limited utility since they can be hampered by transfusion or immunoglobulin therapy. In addition, transplant recipients may not mount an antibody response. Instead, direct detection of virus by qualitative or quantitative DNA PCR is the most useful method. There is no specific antiviral therapy for parvovirus infection although

various management options have been suggested. These consist of a decrease in immunosuppression and/or IVIg. Various dose regimens of IVIg have been used and range from 0.4 to 1 g/kg for 4–10 days.

12.11.3 West Nile Virus

WNV is a flavivirus that has established itself in North America. WNV is most commonly transmitted via mosquito bites but can also be transmitted through blood transfusion and organ donation. Several series of WNV infection transmitted from infected donors to recipients have now been described with the majority of recipients developing encephalitis [128–132]. Donor screening with WNV NAT has been instituted in most organ procurement organizations to reduce the risk of transmission. Donor screening is usually done during periods of high WNV activity or year-round. Community-acquired cases also continue to occur and WNV encephalitis has been described in several kidney and kidney–pancreas transplant recipients [133–136]. A seroprevalence study in organ transplant recipients estimated the risk of neurologic disease to be 40 % compared to <1 % in immunocompetent hosts [137]. Diagnosis of WNV is based on an appropriate clinical picture, a lymphocytic pleocytosis in the cerebrospinal fluid (CSF), and WNV IgM in CSF and serum. A salient feature in transplant recipients is the absence of IgM or delayed positivity. In these cases WNV NAT may be used for diagnosis. There is no specific antiviral therapy for WNV although in the majority of the described cases, immunosuppression was significantly reduced. The successful use of WNV hyperimmune globulin obtained from healthy Israeli blood donors has been described for a liver transplant recipient who developed donor-derived WNV [138]. In addition, IVIg has been successfully used for transplant recipients with WNV [139]. Some studies suggest benefit with ribavirin or interferon-α but this has not been specifically studied in the transplant setting [140, 141]. As a result, many transplant programs advise patients to use personal protection measures such as longsleeved clothing, insect repellent containing *N*,*N*-diethyl-metatoluamide (DEET), and avoidance of outdoor activity at dusk and dawn, a time when mosquitoes are most active.

12.12 Kidney Transplantation in the HIV-Positive Recipient

Traditionally, infection with the HIV was considered to be a contraindication to transplant. However, in the last two decades, the increasing use of HAART (highly active antiretroviral therapy) has significantly increased the life span of HIV-infected individuals [142]. Recent estimates indicate up to 2–17 % of HIV-positive patients have chronic renal disease although rates vary significantly worldwide [143]. A major cause of end-stage renal disease in this population is HIV-associated nephropathy (HIVAN), which is a collapsing glomerulopathy that is more common in African Americans with HIV as well as focal segmental glomerulosclerosis. HIV itself may be a cause of IgA nephropathy. In addition, glomerulonephritis associated with HBV and HCV can also occur in coinfected patients. End-stage renal disease can also be compounded by toxicities of antiretrovirals such as indinavir, tenofovir, and ritonavir.

Recent studies have shown that both graft and patient survival of HIV-infected patients undergoing kidney transplant are similar to HIV-negative patients [144]. However, HIV-infected patients who are coinfected with HCV have significantly lower 5- and 10-year graft and patient survival than HIV-negative/HCV-positive patients [144, 145]. Over time, kidney transplant outcomes for HIV-infected patients have improved [146]. Using the Scientific Registry of Transplant Recipients data from 2003 to 2011, Locke et al. determined that HIV+ patients have a twofold greater risk of acute rejection compared to the HIV-negative group; however, HIV+ patients that received antithymocyte globulin induction had 2.6-fold lower rejection rates than those that received no induction [147]. Acute rejection rates have ranged between 13 and 50 % of patients likely due to variability in patient selection and posttransplant induction and maintenance immunosuppressives [148, 149]. HIV viremia has generally been well controlled. Most centers performing transplants in HIV-positive setting have carefully selected patients for transplant based on CD4 counts, undetectable viral load, and lack of significant opportunistic disease including progressive multifocal encephalopathy, CNS lymphoma, chronic intestinal cryptosporidiosis, and visceral Kaposi's sarcoma [149]. In addition, HIV genotypic and phenotypic testing predictive of suppression on HAART therapy as well as patient compliance are important factors in selection [150].

Posttransplant, drug interactions between immunosuppressives and anti-retrovirals need to be considered. Maintenance immunosuppression consists of steroids, calcineurin inhibitors (CNIs), and MMF. Although both CNIs can be used, patients on tacrolimus had lower rejection rates [149]. There is significant interaction between CNIs and protease inhibitors that inhibit the cytochrome P450-3A system. In this case, CNI doses need to be reduced appropriately. Conversely, CNI doses need to be increased with non-nucleoside reverse transcriptase inhibitors (NNRTIs) such as efavirenz that induce cytochrome P450-3A. Nonetheless, frequent measurement of levels is required to reach the optimal dose. The management of adverse events such as bone marrow suppression is also complicated since HAART, transplant immunosuppressives, and prophylactic antimicrobials (e.g., TMP/SMX, valganciclovir) can be myelosuppressive.

Preventative strategies post kidney transplant in the HIV patient are similar to those in the HIV-negative transplant population with some exceptions. Antipneumocystis pro-

phylaxis is usually given life long rather than the 6- to 12-month prophylaxis regimen used by many centers. TMP/SMX is the standard prophylaxis with alternatives such as dapsone and atovaquone for TMP/SMX intolerance or allergy. Patients with very low CD4 counts may require prophylaxis for other organisms such as mycobacterium avium complex and toxoplasmosis.

Recently, transplantation of kidneys from HIV+ donors into HIV+ recipients has been studied in South Africa where the availability of dialysis is limited [151–153]. In their cohort of 27 transplants, Muller et al. have found 74 % and 84 % patient and graft survival, respectively, at 5-years. At 3-years, the rejection rate was 22 % and HIV viral loads remained undetectable. In the United States, approval of the HIV Organ Policy Equity (HOPE) act in 2013 will allow for increasing research in this emerging area [154]. The field of transplanting HIV-positive patients is relatively young. Changes in selection of patients, optimal immunosuppression regimens, and knowledge of posttransplant infections will increase as results of ongoing studies become available.

12.13 Infectious Risks of Transplant Tourism

Given the limited supply of deceased donor kidneys, a significant proportion of patients from Western countries travel to Eastern countries where kidney transplantation can be performed on a pay basis. Often this involves the illegal trafficking of organs [155]. In this setting, a kidney is harvested from a live donor who needs money to support his/her family or repay debt. The transplant is performed for cash and the patient returns home to be managed by his/her transplant physician. Unfortunately, the standards for organ procurement do not necessarily meet those of registered transplant centers worldwide. Often the patient returns home with no or minimal medical records. Basic information such as donor CMV, EBV, and hepatitis serologies may be unknown. There is an increased incidence of postoperative complications including wound infections, perinephric abscess, colonization, and infection with multidrug-resistant organisms including extended-spectrum beta-lactamase-producing gram-negative bacteria [156–159]. Other issues, although less common, may include malaria (donor-derived or community acquired), donor-derived TB, fungal infections, acquisition of HIV, and hepatitis. To address the issue of organ trafficking and transplant tourism, an international consensus took place in Istanbul that outlined the strategies needed to increase donation and ensure safety of living donors [160]. Physicians caring for individuals who have received transplants in this manner should be aware of the potential exposures.

12.14 Antimicrobials and Nephrotoxicity

Given the unique susceptibility of the allograft to a number of insults, it is reasonable to avoid antimicrobial agents with a high risk of nephrotoxicity. Additive or synergistic nephrotoxicity can occur with antimicrobials and immunosuppressive drugs, especially CNIs. Specific agents that can cause nephrotoxicity include aminoglycosides (e.g., gentamicin, tobramycin, amikacin), intravenous colistin, and standard amphotericin B as well as lipid amphotericin preparations. Routine use of these agents should be avoided especially if an alternative antimicrobial agent can be used. Consideration should be given to the risks and benefits when using these agents with careful monitoring of renal function and drug levels when possible. Other agents such as vancomycin, high-dose TMP/SMX, and high-dose quinolones may be nephrotoxic when combined with potentially nephrotoxic immune suppressants. When possible, antimicrobial levels should be monitored.

12.15 Posttransplant Vaccinations

Vaccinations in renal transplant recipients follow the guidelines for vaccinations in all solid organ transplant recipients [19]. Both inactivated and live vaccines (such as those for VZV (Varivax; Zostavax)) can be given prior to transplant. If the opportunity exists, a vaccine is likely more effective if given pretransplant as early as possible in the course of progressive renal disease. If a live vaccine is given pretransplant, one should wait approximately 4 weeks before transplantation to avoid vaccine-related disease. In the posttransplant period, vaccinations generally begin no sooner than 3–6 months. Although vaccinations could be administered earlier, there are limited data regarding immunogenicity. Yearly influenza vaccine is recommended for all transplant patients. There is no evidence for a link between vaccination and allograft rejection. Renal transplant recipients appear to have a reasonable humoral response to a single dose of influenza vaccine whereas double dose vaccine does not appear to be beneficial [115]. One study showed better graft survival in patients who received influenza vaccine in the first year [161]. Family members and household contacts of the transplant patient should also be vaccinated with annual influenza vaccine. Pneumococcal vaccine is also recommended for renal transplant recipients. In a randomized trial of renal transplant recipients, the pneumococcal conjugate vaccine had an increased trend to greater humoral responses compared to the polysaccharide vaccine [162]. There was a significant decline in titers in the same cohort followed for 3 years with either vaccine [163]. Therefore, most vaccine authorities now recommend one dose of conjugate vaccine followed by one dose of polysaccharide vaccine with a minimum interval of 8 weeks [164]. Other inactivated vaccines generally follow the guidelines for non-transplanted individuals.

12.16 Pneumocystis Prophylaxis

Antimicrobial prophylaxis is recommended post kidney transplant, although there is a wide variety of practices [165]. Prophylaxis for *P. jirovecii* pneumonia (PCP) is generally instituted in the early posttransplant period. PCP appears to be more common in renal transplant recipients who have undergone treatment for multiple rejection episodes and received polyclonal/ monoclonal antibodies [166]. Corticosteroid use has classically been associated with the occurrence of PCP. However, anti- B-cell therapies such as rituximab for the management of antibody-mediated rejection in this population may also increase risk of PCP [164]. PCP prophylaxis is generally instituted for the first 6 months to 1 year posttransplant. Consideration can be given to continuation or reinstitution of prophylaxis beyond this time if the patient remains on high-dose corticosteroids or receives monoclonal antibodies for rejection. In the past 5 years, clusters of late PCP infections have been reported by some investigators suggesting re-emergence of this pathogen [167–169]. The primary agent for prophylaxis is TMP/SMX. Doses used are one single-strength tablet once daily or one double-strength tablet thrice a week. However, a proportion of patients will have toxicity such as leucopenia, rash, and drug-induced hepatitis. In addition, higher doses of TMP/SMX can lead to renal dysfunction. Alternatives to TMP/SMX are once monthly inhaled pentamidine, oral dapsone, or atovaquone [170].

12.17 Summary

In summary, infectious complications continue to be an important cause of morbidity and graft dysfunction in kidney transplantation. With evolving immunosuppression regimens, infectious etiologies are also changing. A prime example of this is BK nephropathy, which has emerged as an important cause of graft loss only in the era of more modern immunosuppression. Traditional infections associated with kidney transplantation, such as CMV, also pose challenges but modern management strategies have reduced the burden of such infections significantly. UTIs and related bacterial infections are very common in these patients and this is an area where clinical trials are needed to better define appropriate therapeutic strategies.

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