Viral Infection after Renal Transplantation: Surveillance and Management

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Viral infections remain a significant cause of morbidity and mortality following renal transplantation. Although cytomegalovirus is the most common opportunistic pathogen seen in transplant recipients, numerous other viruses have also affected outcomes. In some cases, preventive measures such as pretransplant screening, prophylactic antiviral therapy, or post transplant viral monitoring may limit the impact of these infections. Recent advances in laboratory monitoring and antiviral therapy have improved outcomes. This review will summarize the major viral infections seen following transplant and discuss strategies for prevention and management of these potential pathogens.


Despite significant advances in the field of renal transplantation, long-term graft survival has not dramatically increased (1). The reasons for this are varied, but include the persistent impact of infectious diseases on transplant recipients. Viral infections continue to be a potential contributor to graft failure, but also a cause of severe mortality and morbidity (2–6).

The consequences of viral infections are variable and may include direct involvement of the allograft, dissemination to other end organs, or indirect effects on the patient and allograft. Some viruses, notably herpesviruses and polyomavirus, are thought to further impair host defenses, thereby increasing the risk for other infections (4). Viral infections have also been implicated as co-factors in acute and chronic rejection syndromes (2,5,6).

CMV
Cytomegalovirus, a member of the beta herpes virus family, is the most commonly recognized opportunistic pathogen, occurring in 20 to 60 percent of transplant recipients (7). In part this reflects the ubiquitous nature of the virus; in US cities, it is estimated that 60 to 70 percent of the general population demonstrated prior infection with CMV. Consequently the majority of donors and recipients have latent CMV infection at the time of transplantation (8). Moreover, CMV is cell-associated, primarily residing latently in T lymphocytes, although also found in polymorphonuclear cells, endothelial vascular tissue, and renal epithelial cells (9). This cell association allows for transmission of the virus with the transplanted organ.

CMV may have substantial impact on host immune responses. Following infection, CMV infiltrates the cell and produces immediate-early antigens that regulate DNA production. During the ensuing 6 to 24 h, CMV produces late antigens that directly nucleocapsid protein production. It also causes up regulation of IL-2 (IL-2) and can prevent the inhibition of IL-2 gene production by cyclosporine (7). CMV also down regulates MHC-1 molecules on the surface of infected cells to evade host immune recognition (7).

In the general population, with normal immune function, infected individuals can have a range of presenting symptoms, from asymptomatic infection to an infectious mononucleosis like syndrome (9). In the renal transplant population, infection can occur acutely or as reactivation of latent virus. In the absence of prophylaxis, acute infection is most likely to occur between the first and third months following transplant, when immune suppression is at its maximum (10). However, the onset of acute infection has been delayed by the use of prophylactic antivirals in the early post transplant period; currently CMV typically occurs after the cessation of antiviral prophylaxis, later in the first year (Figure 1).

When compared with other organ transplant recipients, renal transplant patients are at lower risk for CMV, in part due to the lower burden of latent virus in the renal allograft. The incidence of CMV in the renal transplant population is estimated to be between 8 and 32 percent (2). Donor seropositivity, especially in the absence of prior recipient infection, is the most important risk factor for post transplant infection. CMV seronegative recipients of seropositive kidneys are at increased risk of invasive CMV disease, recurrent CMV, and ganciclovir-resistant CMV infection (7,11–15).

An increased risk of CMV is associated with increased immunosuppressive exposure, especially to cytolytic agents such as antilymphocyte antibodies, and muromonab anti CD3 (OKT3); all of which promote viral reactivation from latency (10). The presence of rejection and its treatment have also been associated with CMV. Alemtuzumab (Campath) has been associated with an increased risk of CMV viremia in bone marrow transplant populations (16). There is no data currently available that demonstrates that use in renal transplantation increases the incidence of CMV.

The presentation of CMV may be variable, ranging from

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asymptomatic infection (as defined by the presence of active viral replication) to end organ or disseminated involvement. Commonly patients present with symptoms of fever and malaise sometimes associated with leukopenia, thrombocytopenia, gastroenteritis, pneumonitis, hepatitis, or more rarely retinal or uveal involvement. Commonly patients present with symptoms of fever and malaise sometimes associated with leukopenia, thrombocytopenia, gastroenteritis, pneumonitis, hepatitis, or more rarely retinal or uveal involvement.

Patients with CMV appear to have reduced allograft survival (3). Whether this is a direct effect on the allograft or an indirect consequence of infection leading to acute tubular necrosis and cellular rejection has been disputed. Few studies have shown the presence of CMV inclusions in allograft tissue confounding the association of CMV with transplant glomerulonephropathy (7,12). Another study of patients suspected of having CMV disease did not demonstrate a correlation between the degree of viremia and the pathologic presence of virus. Therefore, screening methods for viremia may underestimate the presence of CMV and possibly its impact on the allograft (11). CMV disease has been linked to chronic rejection with arterial myointimal thickening, similar to atherosclerotic coronary disease (7). However, it is still unclear whether the virus itself leads directly to this glomerulonephropathy.

Serologic screening for antibody to CMV should be performed on both donor and recipient before transplant to identify patients at risk for post transplant infection who might benefit from preventive strategies. Two main strategies are employed to prevent CMV. Universal prophylaxis (administration of antiviral medication to prevent infection before its onset) is used for all patients at risk for disease (i.e. those with either seropositive donors and/or recipients) and is continued for a set period of time. Targeted prophylaxis focuses prophylactic strategies on those at highest risk, patients with seropositive donors. An alternative to prophylaxis is a preemptive strategy that employs periodic screening for occult CMV viremia and initiation of early treatment (10). A prospective study of 98 kidney transplant patients comparing preemptive and prophylactic ganciclovir demonstrated that prophylaxis reduced the incidence of CMV infection when compared with a preemptive approach. At the same time, the incidence of severe CMV infection was lower in the preemptive group (18). A recent meta-analysis of 17 prophylaxis trials and 9 preemptive trials using ganciclovir in a variety of solid organ transplant recipients found no statistical significance between the two methods in all-cause mortality or graft rejection outcomes (19). Similarly, a review of recent trials showed no clear beneficial disease or cost difference between the two strategies (20). The choice of preventive strategy varies among institutions and may reflect a cost-benefit analysis (7). A meta-analysis of 32 trials (3737 patients) performed to compare outcomes for various prophylactic antivirals for transplant patients at risk for CMV disease demonstrated that prophylaxis decreased CMV disease, CMV infection and all cause mortality (21). When compared with control groups, prophylactic groups also had a decreased rate of Herpes simplex, Varicella zoster, bacterial and protozoal infections and also decreased acute rejection and graft loss. This meta-analysis showed that ganciclovir was more effective than acyclovir in preventing CMV disease. Valganciclovir and intravenous ganciclovir were found to be as effective as oral ganciclovir for prophylaxis. However, the use of ganciclovir may be associated with a greater rate of CMV resistance when compared with valganciclovir, at least in the highest risk recipients (22,23).

The length of prophylactic treatment varies by institution, but generally lasts for a minimum of 3 mo (11). In high risk patients (D+/R+ and D+/R-) receiving lymphocyte depletion (i.e. ATGAM, Thymoglobulin, OKT3, or CAMPATH), some centers have opted for more prolonged prophylaxis; the optimal duration of prophylaxis is not yet known. With the use of prophylaxis, the onset of CMV disease is usually occurs after the cessation of prophylaxis, consequently delaying the onset beyond the first three months after transplant.

Many techniques are currently available to aid in the diagnosis of CMV disease. Although histopathologic diagnosis remains the gold standard, noninvasive measures of viremia are used more commonly to determine the presence or absence of CMV. The antigenemia assay (detection of lower matrix phosphoprotein pp65 in leukocytes) and nucleic acid testing including CMV-PCR and hybrid-capture DNA are typically used with the choice of methodology varying among centers (7). Many of these newer tests are rapid but are subject to sample degrada-
tion and may need processing within six hours. It is currently not clear if one can correlate extent of disease with the level of viremia in a single assay. Although generally accepted as the most sensitive methodology for CMV detection, nucleic acid testing has not been well-standardized and recent studies have demonstrated substantial interlaboratory variability (8,24). Consequently if CMV is suspected and viremia has not been demonstrated, tissue biopsy of potentially affected organs should be considered.

Treatment of active CMV disease requires a combination of immunomodulation and antiviral therapy. Reduction of immunosuppression, if possible, is an important adjunct to therapy (10). Ganciclovir, the primary antiviral agent used to treat CMV, inhibits CMV replication by inhibiting viral DNA polymerase. In CMV disease, ganciclovir is used at doses of 5mg/kg twice daily (dose adjusted for renal insufficiency) for a minimum of two to three weeks or longer if CMV viremia persists (10). Valganciclovir, a prodrug of ganciclovir, has been used in treatment of CMV retinitis in patients with AIDS but data in transplant recipients is limited (25). In a trial of 21 renal transplant recipients with symptomatic CMV disease and viremia who were treated with Valganciclovir, all cleared their infection and none experienced relapse during a mean follow-up of 5.5 mo (26). Recently, a multicenter randomized control trial was performed with 321 solid organ transplant recipients which demonstrated oral valganciclovir was not inferior to intravenously ganciclovir for the initial treatment of CMV viremia (27).

CMV hyper immune globulin was approved originally as a prophylactic agent to prevent clinically evident CMV disease before the advent of ganciclovir (28). Although it has been used as an adjunctive therapy to treat tissue invasive CMV disease, data are lacking to prove or refute its efficacy.

One of the biggest challenges regarding the treatment of CMV is the emergence of antiviral resistance. Although this is more commonly noted in lung and pancreas transplant recipients, CMV resistance to ganciclovir has been observed in renal transplant recipients. Most commonly resistance emerges due to mutations in the UL 97 gene, which encodes for the first phosphorylation step required for ganciclovir activation. Less frequently, mutations in UL54, the gene responsible for viral DNA polymerase, are seen; in these cases cross resistance to cidofovir and foscarnet can also be observed (7). Ganciclovir resistance should be suspected when patients have persistent, unchanged viremia and/or symptoms at 2 wk into therapy and in such cases, genotypic assays for the detection of the mutations associated with antiviral resistance should be performed. Because UL54 mutations may occur at several sites in the genome and consist of only one bp substitution, phenotypic testing of the virus for various antivirals may be necessary in some circumstances (29). Treatment of resistant isolates may include the use of foscarnet with or without ganciclovir, or cidofovir (10). Small case series have demonstrated some efficacy of leflunomide to treat CMV disease in renal transplant patients (30). A prospective study of 17 patients treated with leflunomide for CMV demonstrated viral clearance and healing of infected organs in 15 patients, or 88 percent (31). In some cases immunoglobulin may be used in conjunction with the antiviral.

**Herpes Simplex Virus and Varicella Zoster Virus**

Herpes simplex (HSV) and Varicella zoster (VZV) are both alpha herpes viruses with a double stranded DNA core. Seroprevalence for HSV-1 in the adult population is as high as 60 percent, while VZV rates can be as high as 90 percent (10,32). Infection in the renal transplant patient is usually caused by reactivation of latent virus. HSV infection usually presents with oral or genital lesions, but in some instances can cause esophagitis, hepatitis, encephalitis or pneumonia (10). VZV reactivation usually presents as dermalomatous zoster, but can disseminate, causing similar visceral complications. In the absence of prophylaxis, HSV and VZV may be seen early with HSV observed even in the first post transplant month and VZV as early as 1 to 6 mo post transplant (Figure 1). The incidence of HSV in renal transplant recipients is estimated to be approximately 53% and VZV 4 to 12% (2).

Pretransplant screening for previous VZV infection should be performed and naive patients should be vaccinated with live attenuated varicella vaccine before transplant whenever possible to avoid primary VZV infection after transplantation, an often severe disease with a high mortality rate (33). However, due to the fact that the VZV vaccine is a live vaccine, the vaccine should not be given if transplant is expected within four to six weeks to prevent active viral shedding at the time of transplant (10). A VZV naive transplant patient who is exposed to someone infected with varicella should receive varicella immune globulin within 96 h of exposure (if available). If VZIG is not available, or the patient presents greater than 96 h following exposure, acyclovir may be considered for postexposure prophylaxis (10). Post-transplant prophylaxis against reactivation of VZV and HSV is recommended to prevent severe recurrences and consists of ganciclovir in patients needing CMV prophylaxis. Those patients who do not require CMV prophylaxis, can receive valacyclovir or acyclovir for approximately one to three months post transplant (10). Recent studies in the immunocompetent host suggest that vaccination with high dose varicella vaccine (Zostavax) may prevent zoster in patients with a prior history of varicella infection (34). Whether this may be effective in transplant recipients is unknown and currently varicella vaccine is not recommended for the previously infected transplant patient and vaccination with live virus vaccines should be avoided in the early post transplant period both to maximize response and minimize adverse events.

Diagnosis may be made with the aid of direct fluorescence antibody for HSV and VZV from vesicular lesions or PCR from CSF or visceral tissue samples. Due to high seroprevalence in the adult population, serologies are rarely helpful in the setting of active infection. Treatment for disseminated infections involves intravenous acyclovir, while less severe infection can be treated with oral acyclovir, valacyclovir, or famiciclovir (10). Acyclovir resistance has been rarely reported in some strains; foscarnet, cidofovir, and topical trifluridine may be considered
for treatment of resistant virus, although careful monitoring of renal function is required (35,36).

**Epstein Barr Virus**

Epstein Barr Virus (EBV) is a gamma herpes virus with a double stranded DNA core; similar to other herpesviruses, EBV remains latent in lymphocytes following primary infection. EBV can cause replication and clonal expansion of the B cells that serve as its primary reservoir and other cell lines as well. However, a competent immune system, specifically T cell response, prevents these cells from propagating. When T cell function is impaired, as is the case in renal transplant patients, this surveillance system can fail and post transplant lymphoproliferative disorder (PTLD) can develop (37). The type of immunosuppression can alter the risk of development of PTLD, with higher incidence rates observed in patients receiving cytolytic therapies, including antithymocyte globulin and OKT3 (38).

The majority of symptomatic infections in renal transplant recipients are primary infection, likely related to reactivation of donor virus (10). Since ninety percent of adults have antibodies to EBV by age 40, symptomatic infection is most commonly seen in pediatric populations. Renal transplants have the lowest risk of acquiring PTLD in comparison with other transplant populations (approx 1 to 3%). PTLD most commonly occurs in the first year post transplant (39) (Figure 1).

Serologies for EBV of both donor and recipient should be obtained before transplant. Allograft recipients who are EBV negative before transplant and receive an organ from a seropositive donor are at greatest risk for PTLD; consequently it is most commonly seen in pediatric and young adult populations. Currently there is no single standard strategy to prevent PTLD. In some centers, high-risk individuals are screened regularly for the presence of EBV viremia and immunosuppression decreased when viremia is observed. Effective prevention of CMV may also prevent EBV infections, primarily by limiting the impact of CMV on immune regulation (40). A recent trial demonstrated that CMV Ig did not prevent the onset of PTLD in high risk recipients (41).

PTLD can be present in many different organs, including the allograft itself and presenting symptoms can vary tremendously based on the site of involvement. Definitive diagnosis of PTLD requires histopathologic confirmation, preferably of tissue obtained by excisional biopsy. In the case of CNS PTLD, analysis of CSF for EBV PCR and cytology should be performed. Although viremia may be noted at the time of PTLD, its detection cannot be used to confirm or refute the diagnosis. Staging is performed by histologic type (monoclonal versus polyclonal, T cell versus B cell) and location (allograft, other organ, metastasis). Often the Ann Arbor classification, used for other non-Hodgkin lymphomas, is utilized (10,35,42).

The optimal treatment for PTLD varies from patient to patient but substantial reduction of immunosuppression can lead to remission in 23 to 86 percent of patients, with a mean response time in those who did respond of 3.6 wk (10,43). Surgical resection may be an option in the renal transplant patient with isolated allograft PTLD, where the graft can be removed and all immunosuppression discontinued. Antiviral therapy with acyclovir or ganciclovir remains controversial as these agents are not active against the latent form of EBV found in PTLD (10). Rituximab, a monoclonal antibody to CD 20 which can be present on many B cell clones in PTLD, is also commonly used for the treatment of PTLD. Response rates vary, but may be as high as 65 percent in solid organ transplant recipients who failed reduction of immunosuppression alone (44). In normal cells, CD20 activates cell cycle initiation and differentiation and also serves as a calcium ion channel (45). The mechanism of action of rituximab is not clearly understood but there are several prevailing hypotheses. Research has demonstrated that complement dependant cytotoxicity, antibody dependent cellular cytotoxicity, and initiation of apoptosis may all play a role in its efficacy (45).

In patients that fail these strategies, IFN and IVIG have been used with varying success (10). Cytotoxic chemotherapy has been used as salvage therapy (10). The substantial reduction in immunosuppression required for treatment of PTLD may result in allograft loss; however in patients who experience a complete remission, retransplantation has been successful (46). Outcomes with PTLD in renal transplant recipients vary depending on the site of involvement. Patients with isolated allograft involvement have a five year survival of approximately 68% compared with those patients with PTLD extending beyond the transplanted kidney whose five year survival varied between 36 and 38 percent (47).

**Human Herpesvirus-6, Human Herpesvirus-7, and Human Herpesvirus-8**

The significance of Human Herpes virus 6 and 7 following renal transplantation is controversial. Similar to other herpesviruses, these beta herpes viruses are common causes of fever in normal children. Following primary infection they remain latent in lymphocytes. In the transplant population, disease is postulated to occur as a result of reactivation in the first 4 wk after transplant in individuals who are not receiving prophylaxis for CMV (48) (Figure 1). Presenting features are similar to those of CMV and may include fever, leukopenia, hepatitis, and encephalitis.

Diagnosis requires demonstration of the virus either by nucleic acid testing of peripheral blood lymphocytes or immunohistochemistry of biopsy tissue samples (35,48). Often, HHV-6 viremia is discovered in conjunction with other viral pathogens, such as CMV, and it has been hypothesized that HHV-6 may be a cofactor promoting other viral infections including CMV because of its own immunomodulatory effects (48–50). However, it remains unclear whether HHV-6 or 7 actually causes disease, promotes other viral infections, or simply activates without sequelae. Some small prospective studies have demonstrated that these viruses may be mediators of graft rejection (51,52). Treatment is similar to CMV and should involve reduction of immunosuppression and ganciclovir, but cidofovir and foscarnet have also been utilized (10,35,49).

Human Herpes Virus 8 (HHV8) is a gamma herpes virus that has been associated with Kaposi’s Sarcoma, primary effusive lymphoma, and Multicentric Castleman’s Disease (lymphopro-
liferative disorder). Infection in the renal transplant population is thought to most commonly happen through reactivation of latent virus, although primary infection after transplant can occur and can be acquired through the allograft itself (53,54). Kaposi’s sarcoma is the most common presentation of HHV8 in renal transplant recipients, with an incidence varying from 0.2 percent in some North America centers to up to 5.3 percent in Saudi Arabian transplant centers, reflecting the tremendous geographic variability in infection (54,55).

HHV-8 is thought to lead to Kaposi’s Sarcoma through upregulation of vascular endothelial growth factor (VEGF) receptor Flk1/KDR in endothelial cells (56). Therapy for KS includes reduction of immunosuppression and cytotoxic chemotherapy. Recently smaller case series and reports suggest that sirolimus may be effective treatment for Kaposi’s Sarcoma. It is thought that sirolimus inhibits not only production of VEGF but also dampens its effects on endothelial cells (56). Case reports demonstrate regression in KS tumors when immunosuppression is changed to Sirolimus or with the use of foscarnet (55–58). Further studies regarding the optimal treatment for transplant patients are needed.

**BK and JC Virus**

First described in a renal transplant recipient with ureteral stenosis, BK virus, a small circular double stranded DNA virus and member of the polyomaviridae, has recently been recognized as an important cause of renal allograft impairment. Sixty to eighty percent of the adult population demonstrates serologic evidence of prior infection with either BK or JC (another polyomavirus); consequently the majority of post transplant BK infections are thought to stem from reactivation of latent virus in the allograft (59,60). JC virus can be found in multiple sites including bone marrow and the central nervous system and is a less common cause of post transplant infection (60,61). Probably because of its latency in the kidney, BK rarely affects nonrenal transplant recipients; JC infections do not have the same specificity and have been observed in all recipients of solid organ transplants.

Until recently, polyomavirus infections were uncommon sequelae of transplantation. However rates of infection in renal transplant patients have increased, now ranging from ten to sixty percent (10,60). BK virus typically involves the allograft kidney, with manifestations including interstitial nephritis, utereral stenosis, and ureteral stricture (10,62). Bone marrow transplant recipients have shown evidence of hemorrhagic cystitis from BK virus, but this has not been demonstrated in the renal transplant population.

The recent increase in BK infections has been attributed, in part, to the use of more potent immunosuppressive regimens. However, no specific immunosuppressant medication or combination has been demonstrated to increase the risk of nephropathy. Caucasian race, cadaveric renal transplant, older age, presence of diabetes, and combined kidney and pancreas transplants have all been shown to be associated with BK virus nephropathy (63,64). Most commonly, infection occurs within the first three to four months after transplant, when immunosuppression is at its highest (65). Infected patients present with a rise in serum creatinine, which can be acute or more gradual. Fever may occur but is not consistently observed and often the presentation of disease may mimic acute rejection.

Although JC virus has been rarely implicated as a cause of nephropathy either alone or in combination with BK, it is more commonly seen as a cause of Progressive Multifocal Leukoencephalopathy, a demyelinating process involving the cerebral white matter (66,67). Presenting symptoms include progressive neurologic impairment, which can progress to dementia (67,68).

Due to its ubiquitous nature, currently there are no recommendations for screening donors or recipients for BK or JC virus before transplant, although many centers periodically screen patients for BK to both screen for evidence of over immunosuppression and allow for reduction of immunosuppression before the development of irreversible renal damage. Blood nucleic acid testing for viremia is the most sensitive noninvasive method for detection of nephropathy (65). If screening tests are positive with no evidence of renal dysfunction, immunosuppression should be decreased whenever possible to allow for recovery of host defenses necessary to combat infection (65). In the setting of an elevated creatinine, a renal biopsy should be obtained looking for consistent histopathologic changes; immunohistochemistry or in situ hybridization for BK viral proteins. The mainstay of treatment for polyoma virus infections has been reduction in immunosuppression. This has been shown to eliminate viremia in patients without allograft dysfunction. However, if a patient has persistent BK virus infection and renal dysfunction that is not improving, the addition of antiviral agents should be considered, although optimal treatment in this setting is unknown. Limited data suggest that leflunomide and/or cidofovir may be effective in the treatment of some patients with BK nephropathy (69). There is very limited data on the use of fluoroquinolone antibiotics and IVIG and further study is needed to test the effectiveness of these treatments (65). To date no antiviral agents have been demonstrated to be effective in the treatment of PML.

**Hepatitis B and C**

Patients with chronic renal failure, notably those receiving hemodialysis, may be at increased risk for Hepatitis B. Consequently all nonimmune patients with chronic renal failure should be vaccinated with Hepatitis B vaccine and immunity verified with Hepatitis B surface antibody screening following completion of the vaccination series (70). Currently, it is estimated the prevalence in the HD population ranges from 0.1 to 0.4 percent (10). Approximately 2 to 10 percent of patients with a history of Hepatitis B before transplantation will reactivate post transplant.

The appropriate Hepatitis B vaccination regimen in end stage renal disease (ESRD) patients has been studied and several methods have been developed including using higher vaccine doses and intradermal injections of vaccine. A recent study of 52 patients examined the use of recombinant Hepatitis B vaccine (Engerix-B) injected every 2 wk at 20 μg until adequate antibody titers were achieved. If antibody levels dropped below 20 IU/L, a reinforcement vaccine was administered.
monothly until titers returned to appropriate levels. Their results demonstrated an earlier peak of Hepatitis B surface antigen (3.9 ± 1.7 mo) and cumulative seroconversion rate of 96.9% after one year at a cost of 127.7 Euros per patient for a two year period (71). A study of 24 renal transplant recipients who did not respond to intramuscular vaccine had an overall response rate of 63% to a series of eight intraderal vaccinations followed by an intramuscular injection (35). A retrospective study of 64 ESRD patients demonstrated that patients given higher dose recombinant Hepatitis B vaccine (Engerix-B, 80-μg) had increased likelihood of persistent protective antibody compared with those who received lower dose vaccine (72).

Previously, patients who were Hepatitis B surface antigen positive were not considered to be acceptable candidates for transplantation; however the more recent availability of effective antiviral agents has allowed consideration of the recipient with chronic Hepatitis B who has cleared viremia. In one case series of 151 renal transplant patients who were Hepatitis B surface antigen (HBsAg) positive at the time of transplant, a higher percentage of histologic degradation and increased risk of liver mortality was seen but there was no difference in overall mortality rates when compared with HBsAg negative transplant patients (73). Although there is some controversy, recent studies suggest an overall decrease in graft survival at ten years when compared with matched controls for renal transplant patients who are Hepatitis B sAg negative (74,75). For patients who are surface antigen positive, a liver biopsy should be obtained before and after transplant to evaluate the extent of liver disease (10).

As with other viral infections, treatment of chronic hepatitis B includes reduction of immunosuppression whenever possible. Optimal therapy should include the use of at least one antiviral active against Hepatitis B; currently lamivudine is most commonly used. Studies in nontransplant patients have demonstrated a remission rate of approximately 68 percent when using lamivudine as monotherapy. However, at 24 mo after treatment, the remission rate had decreased to approximately 41 percent due to the emergence of YMDD mutations (76). Alternative antivirals with activity against Hepatitis B include IFN, adefovir, entecavir and telbivudine. Because of the potential for renal toxicity, these potentially more effective agents are not commonly used in renal transplant recipients. Further study may be helpful to determine optimal management of Hepatitis B following transplantation. It is important to note that withdrawal of antiviral therapy may result in an exacerbation of liver disease and consequently should be avoided (10,75,77).

The use of hepatitis B surface antigen positive donors confers a high risk of hepatitis B acquisition in the recipient. However, transplantation using hepatitis B surface antigen positive donors has been performed and post transplant treatment with Hepatitis B immune globulin and lamivudine has been used with success in case reports (10). Small case series have reported successful outcomes using Hepatitis B surface antigen positive renal transplant donors for surface antigen positive recipients (78). Of note, the use of donors with isolated Hepatitis B core antibody positivity in recipients with no prior history of Hepatitis B demonstrates a very low risk of Hepatitis B transmission and no significant impact on patient or graft survival (79,80). Recommendations for using Hepatitis B core antibody positive donors include testing donors for Hepatitis B viral DNA with lamivudine administration to treat recipients until the results return. If the Hepatitis B DNA test is negative, lamivudine can be discontinued (81). In the future, more studies are needed to determine if the use of donors with chronic hepatitis B will be safe in larger groups of patients.

Similar to Hepatitis B, Hepatitis C is a complex problem for the renal transplant recipient. Incidence rates in the HD population have decreased, averaging 0.7 to 3 percent per year (10). Recognition of Hepatitis C in patients with chronic renal failure may be confounded by the limited sensitivity of serologic diagnosis in this population. All Hepatitis C seronegative transplant candidates who have abnormal transaminases and/or risk factors for Hepatitis C (including a history of parenteral drug use or transfusion before screening of blood products for Hepatitis C) should undergo nucleic acid testing (70). Because of the increased risk of progressive liver disease following transplantation, patients with Hepatitis C should undergo liver biopsy to exclude advanced liver disease, which in some cases may necessitate a combined liver-kidney transplant.

Hepatitis C positive patients usually have a marked rise in viral load with initiation of immunosuppression immediately post transplant. Chronic immunosuppression used in transplant recipients also leads to higher circulating levels of virus and intrahepatic virus due to the decreased T cell response to Hepatitis C virus (10). Consequently patients with Hepatitis C are at increased risk for progressive liver disease and the development of cirrhosis following transplantation.

Because of the large demand for organs, consideration has been given to the use of Hepatitis C positive donors. Transplant recipients may acquire hepatitis C through transplantation itself, which may lead to severe hepatitis. Although recipients of HCV positive kidneys have diminished patient and graft survival as compared with recipients of HCV negative kidneys, survival may be improved when compared with survival on dialysis (82).

Treatment for hepatitis C in the general population usually consists of a combination of IFN and ribavirin. Ribavirin is metabolized in the kidney and should not be used in patients with a creatinine clearance less than 50, as severe side effects including hemolytic anemia can occur. Before transplant, treatment with IFN has been shown to decrease viral loads and decrease liver disease morbidity in hemodialysis patients and should be initiated if possible (83). Although pegylated IFN has been used more recently with improved outcomes in the treatment in hepatitis C, concerns about toxicity prohibit its use in those on hemodialysis (10). A prospective study of 29 renal transplant candidates with Hepatitis C demonstrated a 64.2% virologic response in those receiving IFN. Of the 14 patients who received a transplant, 8 patients continued to have negative Hepatitis C viral RNA levels at 41 mo after transplant (84). Post transplant, IFN treatment has been linked to acute graft rejection when studied as a treatment for CMV infection (74,85).
However recent studies in liver transplant recipients have not demonstrated significant rejection, thus this could potentially be considered for treatment of Hepatitis C in the renal transplant population. One recent prospective study examined the use of low dose IFN in 11 renal transplant patients, of which 8 completed a full course of treatment. Of the eight patients, 5 cleared their Hepatitis C viremia and sustained biochemical and virologic responses were seen in 3 patients (86). More data are needed before the widespread implementation of IFN in this setting. Little is known about treatment with ribavirin alone post transplant; some studies have shown histologic improvement in liver inflammation while others have shown worsening fibrosis (87–89). A recent prospective study used ribavirin monotherapy in 13 renal transplant patients with severe fibrosis. Although there was no significant change in Hepatitis C viral load, a significant decrease in transaminase level and the combined fibrosis and inflammation score (Metavir score) (90). Further studies are needed to see if this is a viable treatment option.

**Human Immunodeficiency Virus**

With the advent of highly active antiretroviral therapy (HAART), HIV infected patients now have improved overall survival rates, but increased morbidity and mortality from other chronic conditions including end stage renal disease. Initially HIV infected individuals were not considered to be appropriate candidates for transplantation as early studies demonstrated an increased risk of mortality following transplantation in HIV infected individuals (10). However, more recent studies have suggested that HIV patients receiving HAART have improved survival compared with historical controls. Moreover, patients did not experience significant HIV related complications following transplantation (91,92). A recent retrospective study was performed comparing 38 HIV positive renal transplant recipients compared with 38 HIV negative recipients who received organs from the same donor. There was no statistically significant difference in graft or patient survival between the two groups (93).

Highly active antiretroviral therapy consists of a combination of medications, some of which are associated with inhibition or induction of cytochrome P450, impacting on levels of calcineurin inhibitors and TOR inhibitors. Patients receiving protease inhibitors typically experience marked inhibition of cytochrome P450 and consequently require miniscule doses of calcineurin inhibitors. Optimal tacrolimus dosing may be as low as 1mg per week if used concomitantly with protease inhibitors. Non nucleoside reverse transcriptase inhibitors can either inhibit or promote activity of P450. This can affect levels of calcineurin inhibitors if not dose adjusted. Mycophenolate may also affect the patient’s antiretroviral regimen by increasing levels of abacavir and didanosine but decreasing levels of cidofovir may have activity against adenovirus, but its use for severe rejection, thus this could potentially be considered for treatment of Hepatitis C in the renal transplant population. One recent prospective study examined the use of low dose IFN in 11 renal transplant patients, of which 8 completed a full course of treatment. Of the eight patients, 5 cleared their Hepatitis C viremia and sustained biochemical and virologic responses were seen in 3 patients (86). More data are needed before the widespread implementation of IFN in this setting. Little is known about treatment with ribavirin alone post transplant; some studies have shown histologic improvement in liver inflammation while others have shown worsening fibrosis (87–89). A recent prospective study used ribavirin monotherapy in 13 renal transplant patients with severe fibrosis. Although there was no significant change in Hepatitis C viral load, a significant decrease in transaminase level and the combined fibrosis and inflammation score (Metavir score) (90). Further studies are needed to see if this is a viable treatment option.

**Respiratory Viruses**

Various viruses can cause respiratory disease in the renal transplant population, including adenovirus, respiratory syncytial virus, influenza, parainfluenza, human metapneumovirus, rhinovirus, and coronavirus (10). These viruses can lead to upper respiratory tract disease, as well as bronchitis, pneumonia and pneumonia. Adenovirus can cause a multitude of complications including gastroenteritis, cystitis, and necrotizing hepatitis in addition to respiratory illness. In the renal transplant recipient, adenovirus can also cause nephritis, which presents with fever, renal dysfunction, and liver function test abnormalities (96,97). Infection with respiratory viruses may also be associated with rejection. Severity of disease is greatest in those who have been more recently transplanted or are more immuno suppressed. Prevention involves avoidance of other individuals who have signs or symptoms of infection, hand hygiene, and use of droplet precautions for those suspected of having infection.

Influenza vaccine should be administered pretransplant and every year after transplant, although administration should not be given in the early post transplant period because of especially reduced vaccine responses (10). Regardless of vaccine timing, vaccine responses are reduced in transplant recipients with notable reduction of antibody responses in patients receiving mycophenolate (98–100). Because the vaccine may be insufficiently protective in the patient post transplant, the influenza vaccine should also be administered to the patient’s family members and to health care providers to decrease possible risk of transmission. Intranasal influenza vaccine should not be used, as it is utilizes live virus.

Treatment of respiratory viral infections involves supportive care and, in some cases, the use of antiviral medications. Influenza can be treated with oseltamivir or zanamavir, which will treat both influenza A and B. Amantadine is not recommended because it treats influenza A only and increasing rates of resistance have been seen in influenza A. Ribavirin is approved to treat lower respiratory infection with respiratory syncytial virus; however actual clinical efficacy has not been proven (10). Severe Adenovirus infections are usually treated with reduction of immunosuppression. Anecdotal reports suggest that cidofovir may have activity against adenovirus, but its use must be balanced with the associated risk of nephrotoxicity (101).

**West Nile Virus**

West Nile Virus is a flavivirus that causes a febrile illness, associated with encephalitis, and can be fatal (10). Reports have demonstrated that it is transmissible through organ transplantation and that transplant recipients who acquire West Nile Virus from their donors have increased morbidity and mortality (102–104). Recipients who acquire West Nile later in the
transplant course have more variable outcomes (105). To prevent infection, seasonal screening should be considered for donors before transplant by serologic and/or nucleic acid testing. Additionally all transplant recipients should be counseled in preventive measures regarding mosquito bites, including the use of protective clothing and DEET containing insect repellants. Treatment for West Nile in transplant recipients has not been standardized but should include a reduction in immunosuppression along with supportive care (103). Whether there is a role for hyperimmune globulin in transplant recipients is currently unknown.

Viral infections in renal transplant patients continue to have significant impact on patient outcomes. Although preventive measures have improved, the impact of newer immunosuppressive strategies continues to promote the development of severe viral infections. The presence of new and emerging viral infections that may be transmitted by transplantation, such as West Nile virus, will likely present many future challenges for physician treating transplant recipients.

Disclosures

None.

References

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