



Management strategies for common viral infections in pediatric renal transplant recipients

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Abstract

Viral infections have been considered as a major cause of morbidity and mortality after kidney transplantation in pediatric cohort. Children are at high risk of acquiring virus-related complications due to immunological immaturity and the enhanced alloreactivity risk that led to maintenance of high immunosuppressive regimes. Hence, prevention, early detection, and prompt treatment of such infections are of paramount importance. Among all viral infections, herpes viruses (herpes simplex virus, varicella zoster virus, Epstein-Barr virus, cytomegalovirus), hepatitis B and C viruses, BK polyomavirus, and respiratory viruses (respiratory syncytial virus, parainfluenza virus, influenza virus and adenovirus) are common in kidney transplant recipients. These viruses can cause systemic disease or allograft dysfunction affecting the clinical outcome. Recent advances in technology and antiviral therapy have improved management strategies in screening, monitoring, adoption of prophylactic or preemptive therapy and precise treatment in the immunocompromised host, with significant impact on the outcome. This review discusses the etiology, screening and monitoring, diagnosis, prevention, and treatment of common viral infections in pediatric renal transplant recipients.

Key Words: Viral infections; Post renal transplant; Immunosuppressive regimes; Herpes simplex virus; Varicella zoster virus; Epstein-Barr virus; Cytomegalovirus; Hepatitis B virus; BK polyomavirus; Viral monitoring

Core Tip: Pediatric renal transplant recipients are at high risk of acquiring virus-related complications due to immunological immaturity and the enhanced alloreactivity risk that led to maintenance of high immunosuppressive regimes. Prevention, early detection, and prompt treatment of such infections are important. Recent advances in technology and antiviral therapy have improved management strategies in screening, monitoring, adoption of preemptive therapy and precise treatment in the immunocompromised host, with significant impact on the outcome.

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INTRODUCTION

Renal transplantation is a life-saving yet cost-effective treatment modality for children having end-stage kidney disease[1, 2]. More effective and potent immunosuppressive strategies have resulted in improved graft survival amongst renal transplant recipients receiving histo-incompatible grafts. However, immunosuppression has its own costs which can result in increased risk and severity of specific viral infection itself, infections by opportunistic bacteria and immunomodulating viruses[3]. These infections may result from reactivation of latent viruses due to immunosuppression or transmission from a donor allograft. These viral infections have the potential to cause damage to the allograft and acute rejection adding to increased morbidity and mortality[4] and poor graft and recipient outcomes over long run.

Thus, it is of paramount importance to develop effective strategies to control post-transplant viral infections. This needs considerable effort in establishing a viral monitoring mechanism which should be feasible and cost-effective. Formulating a sensitive, specific and reliable diagnostic assay using quantification of viral load is essential for the clinical utility of viral monitoring. Recent advances in technology and antiviral therapy have improved management strategies in screening, monitoring, adoption of prophylactic or preemptive therapy and precise treatment in the immunocompromised host, with significant impact on the outcome. This review discusses the etiology, screening and monitoring, diagnosis, prevention, and treatment of common viral infections in pediatric renal transplant recipients.

ETIOLOGY

Viral infections are one of the common complications seen amongst children following renal transplantation. A child can acquire viral infections following the renal transplantation through several mechanisms and these infections account for significant mortality and morbidity. Blood products and donor allografts act as potential sources of viral infection whilst the reactivation of viruses present in the recipient can occur due to heavy immunosuppression.

Common viral infections in renal transplant recipients include cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes simplex viruses, varicella-zoster virus (VZV), respiratory viruses (respiratory syncytial virus, parainfluenza virus, influenza virus and adenovirus), hepatitis B and C viruses, and human BK polyomavirus (BKPyV)[5].

Cytomegalovirus

Cytomegalovirus infection is highly prevalent globally and most primary infections occur in early childhood and are generally asymptomatic[6]. Transplant recipient is at a higher and constant risk for severe cytomegalovirus infections following immunosuppression. These infections are caused by several mechanisms including reactivation of a latent infection, superinfection of the donor graft and primary infections. The patients are particularly at a higher risk if they are seronegative for CMV and received a seropositive donor kidney[7] or receive treatment with lymphocyte depleting antibodies (e.g. anti-thymocyte globulin)[8]. The symptoms due to CMV are caused by viral replication within the immunocompromised host, cytopathic effect and organ spreading[9]. The severe clinical manifestations range from gastrointestinal manifestations such as colitis, oesophagitis and other organ effects such as myocarditis, hepatitis, retinitis and pneumonitis[10]. Endothelial damage, vasculopathy and immunomodulation caused by CMV leads to secondary opportunistic infections such as severe fungal disease[11] and listeriosis[12].

Epstein-Barr virus

Most children acquire primary EBV infection during early years of life and EBV results in a self-limiting clinical syndrome commonly known as infectious mononucleosis. EBV has the ability to remain within dormant following primary infection and reactivate in the presence of impaired T-cell immunity[13]. The most significant complication that occurs following EBV infection is post-transplant lymphoproliferative disorder that carries a mortality as high as 50%[14].

Polyomavirus BK

Polyomavirus associated nephropathy can lead to graft dysfunction and loss and is one of the serious complications seen in kidney transplant recipients[15]. The virus replicates in renal tubular epithelium and urothelium and higher viral replication rates are a strong risk factor for nephropathy in the grafted kidney[16]. Highest incidence of nephropathy is seen during the first year following transplantation[17].

Herpesvirus 6

Herpesvirus remains latent following the primary infection and reactivation following immunosuppression during the post transplantation period can result in serious complications such as bone marrow suppression, cholestatic hepatitis and interstitial pneumonitis[18].

Respiratory viruses

Respiratory viruses are the most common as a single group seen amongst children who are kidney transplant recipients [19]. Influenza viruses, respiratory syncytial virus, adenoviruses, and parainfluenza viruses are the most common respiratory viruses[20]. Immunosuppression often leads to a prolonged course and are associated with an increased risk of complications following these viral infections.

Varicella zoster virus

Primary infection is rare following immunization, but can lead to severe disease with high morbidity and mortality. Reactivation of primary varicella zoster infection leading to herpes zoster is seen more commonly in transplant recipients. The risk for herpes zoster is increased by use of lymphocyte depleting agents as immunosuppression, lack of anti-CMV prophylaxis and low natural killer cells counts[21,22].

Hepatitis B and C viruses

Children with renal transplant, notably those received hemodialysis, may be at increased risk for Hepatitis B and C. Enhanced viremia following immunosuppression would lead to reduce graft survival and increased liver mortality[23, 24].

SCREENING AND MONITORING

Detection of CMV antigenemia by means of identification of lower matrix phosphoprotein pp65 in CMV-infected leukocytes is widely used for screening and monitoring of cytomegalovirus in transplant recipients[25]. Detection CMV DNA titers is performed by quantitative nucleic acid amplification testing. These methods are used to guide preemptive therapy following renal transplantation. In high-risk recipients (CMV IgG +ve donor (D+)/ CMV IgG -ve recipient (R-), CMV polymerase chain reaction (PCR) should be monitored monthly for 3-6 mo and then, 3 monthly during the first year following transplantation. Subsequent CMV PCR should only be requested in response to clinical need. The CMV IgG negative patients should have annual CMV serology until positive (Table 1).

The main complication seen in patients with EBV infection is post-transplantation lymphoproliferative disorder. Although this complication is seen less frequently compared to most other solid organ transplant recipients, the risk is increased with longer duration of immunosuppression and in those with high-risk (donor EBV seropositive/recipient seronegative) renal transplant recipients. It is recommended that all seronegative patients who undergo kidney transplantation are monitored for EBV DNA titers in their plasma[26]. Kidney disease Improving Global Outcomes clinical practice guideline recommend that monitoring high-risk (donor EBV seropositive/recipient seronegative) renal transplant recipients for EBV PCR: Once in the first week after transplantation; monthly for the first 3-6 mo after transplantation; then 3 monthly during the first year following transplantation. EBV R+ patients do not generally need frequent monitoring to detect EBV DNA in plasma.

Early diagnosis of polyomavirus associated nephropathy is crucial in improving graft outcomes. This necessitates renal biopsy and demonstration of polyomavirus related interstitial nephritis and cytopathic changes[27]. Although polyomavirus viremia precedes viraemia by several weeks due to predominant proliferation of the virus in the urothelium, the correlation with viremia and nephropathy is poor. Therefore, detection of viraemia by quantitative PCR on plasma is considered most predictive for screening for development of polyomavirus associated nephropathy[28]. On the contrary, negative viremia has a higher negative predictive value and viremia may be used as a first line screening test in suspecting early nephropathy[29]. However, given the limited specificity of viremia, it is required to establish the nephropathy before deciding to reduce the immunosuppression. Although the practices can vary across institutions, it is generally recommended to monitor the viral activity monthly for first 3 mo, 3-monthly thereafter during the first year, 6-monthly during the second year and annually thereafter during the first five years following transplantation[15].

Reactivation of hepatitis B virus (HBV) after transplantation is a major concern. Markers to detect hepatitis B infection include positive HBsAg and antibody to hepatitis B core antigen (Table 2). HBV serology testing in donors is important in reducing the risk of post-transplant infections. Screening for Hepatitis C sero-positivity using anti-HCV antibodies should be performed in all transplant candidates.

Table 1 Pre-transplant screening and diagnostic work-up for kidney transplant recipients

CMV	CMV IgG serology in both donors and recipients
EBV	Screening by EBV serology in both donors and recipients
BKPyV	Not done at present
HSV	HSV antibodies in blood
VZV	Pretransplant screening for previous VZV infectio
Hepatitis B & C	HBV
	HBsAg and antibody to hepatitis B core antigen (antiHBc)
	HCV
	HCV antibody test
Respiratory viruses	Nasopharyngeal wash or bronchoalveolar lavage fluid (BAL) specimens (in the case of Adeno virus - stools or plasma), by conventional viral culture, PCR, or direct immunofluorescence

CMV: Cytomegalovirus; EBV: Epstein-Barr virus; BKPyV: Human BK polyomavirus; HSV: Herpes simplex viruses; VZV: Varicella zoster virus; HBV: Hepatitis B virus; HCV: Hepatitis C virus.

Table 2 Post-transplant screening and diagnostic work-up for kidney transplant recipients

CMV	Quantitative CMV viral load
	Diagnosis- presence of CMV DNA in whole blood or plasma
	Tissue biopsy
	Diagnosis- presence of CMV inclusion or immunostaining
	CMV serology
	Diagnosis- presence of CMV IgG post kidney transplantation in
	CMV R- patients
EBV	Quantitative EBV viral load
	Tissue biopsy
	EBV serology
BKPyV	Urine cytology
	Quantitative BK viral load in urine
	Quantitative BK viral load in plasma
	Allograft biopsy
HSV	Direct fluorescence antibody for HSV from vesicular lesions or PCR from CSF or visceral tissue samples
VZV	Direct fluorescence antibody for VZV from vesicular lesions or PCR from CSF or visceral tissue samples
Hepatitis B & C	HBV
	HBsAg and antibody to hepatitis B core antigen (antiHBc)
	HCV
	HCV antibody test
Respiratory viruses	Nasopharyngeal wash or bronchoalveolar lavage fluid (BAL) specimens, (in the case of Adeno virus - stools or plasma), by conventional viral culture, PCR, or direct immunofluorescence

CMV: Cytomegalovirus; EBV: Epstein-Barr virus; BKPyV: Human BK polyomavirus; HSV: Herpes simplex viruses; VZV: Varicella zoster virus; HBV: Hepatitis B virus; PCR: Polymerase chain reaction.

DIAGNOSIS

Cytomegalovirus infections are diagnosed with either detection of CMV antigenaemia or nuclear amplification techniques to determine CMV DNA titers. Immunodiagnostic methods such as determination of CMV specific IgM or IgG antibodies are useful in CMV infections mainly during the first year following transplantation. Resistant CMV infections often need more advanced testing such as genotypic resistance testing to detect resistant strains of CMV.

The diagnosis polyomavirus BK viraemia is made demonstration of viral DNA in plasma. The polyomavirus associated nephropathy is confirmed by renal biopsy to demonstrate cytopathic changes characteristic of the viral proliferation in the presence of positive viral DNA in plasma. Plasma DNA level is used for determining treatment thresholds.

Due to high prevalence of Herpesvirus 6 in otherwise healthy children, detection of active replication distinctly from existing primary infection can be challenging. Quantitative PCR assays and biopsy of the grafted kidney are helpful in diagnosing active replication[30]. PCR also has an additional advantage over serological tests to differentiate A and B subtypes of HHV6.

Most respiratory viruses are diagnosed by quantitative PCR, viral culture or immunodiagnostic methods from samples such as nasopharyngeal aspirate or bronchoalveolar lavage. Adenovirus can be found in other specimens such as plasma and stools.

Diagnosis of HBV infection is with detection of Hepatitis B Surface antigen and antibodies to Hepatitis B core antigen. This should be followed up with quantification of viral load by PCR. Anti- HCV antibodies and quantitative PCR are used to diagnose Hepatitis C infection.

TREATMENT

Infections need vigorous and timely treatment to prevent severe complications in the immunocompromised transplant recipient. CMV infections are treated depend on the viral load and clinical symptoms (Table 3). Intravenous ganciclovir or oral valganciclovir are first line treatment and intravenous ganciclovir is preferred in the presence of severe infections, higher viral titers and poor gastrointestinal absorption. A minimum of two-week course is recommended and treatment should be guided by viral clearance and resolution of symptoms. Resistant CMV infection is diagnosed when either clinical symptoms or viraemia persists despite 2-wk course of ganciclovir[31]. Optimization of antiviral therapy and reduction in immunosuppression as necessary and deemed safe are also important in treating resistant CMV infections. Foscarnet is the drug of choice for those with mutations in *UL97* gene which is associated with higher resistance for conventional treatment[32]. It is recommended that antiviral therapy is continued until complete symptomatic recovery, virologic clearance and at least 2-wk course of anti-viral therapy is administered[33].

Early diagnosis and commencement of treatment is crucial in improving outcomes of patients with post-transplantation lymphoproliferative disorder following EBV infection. Persistent symptoms of lymphoproliferative syndrome or mononucleosis like syndrome should make the clinician suspect post-transplant lymphoproliferative disease (PTLD). However, it is recommended that histological diagnosis is made in order to determine the appropriate treatment regimen [34]. Widely accepted modalities of treatment of PTLD include reduction in immunosuppression, local irradiation or surgical excision and use of chemotherapy[26]. In life-threatening and extensive PTLD, abrupt reduction in immunosuppressive therapy is required to prevent mortality and this mainly involves discontinuation antimetabolite agents, calcineurin inhibitors and other non-corticosteroid immunosuppressive agents[34]. Rituximab is also considered standard therapy for CD 20 positive B cell post-transplantation lymphoproliferative disorder.

Polyomavirus associated nephropathy is primarily treated by either reduction or switching of the immunosuppressive regimen. Use of antiviral agents has not proven to be efficacious[35]. However, in the presence of rise of creatinine and renal dysfunction, the treatment should be guided by the renal biopsy findings. Widely used interventions for Polyomavirus associated nephropathy include stepwise reductions in doses of calcineurin inhibitors, antimetabolites and switching tacrolimus to cyclosporin A[36,37]. However, these practices may vary in different centers.

Successful treatment of Herpesvirus 6 has been achieved by use of either ganciclovir or foscarnet combined with reduction in immunosuppressive therapy as necessary[38]. However, treatment can be complicated in some children due to emergence of viral strains that are resistant to ganciclovir[39].

Treatment of choice for respiratory viruses following immunosuppression is Ribavirin[40,41]. However, it has proven efficacy only against respiratory syncytial viruses. There are reports of intravenous cidofovir being used successfully to treat adenoviral infections[42] and more evidence in this regard is necessary.

Treatment of HBV infection includes reduction of immunosuppression with the combination of at least one antiviral active against HBV infection. The lamivudine is the most common drug used at present. Other antivirals with activity against Hepatitis B include interferon (IFN), adefovir, entecavir and telbivudine should be used with caution due to potential for renal toxicity. With the emergence of effective antiviral agents, patients positive for HB surface antigen and antibodies for Hepatitis B core antigen are considered as renal transplant recipients provided that they are cleared of viremia after therapy. These recipients should undergo liver biopsy before and after transplantation to evaluate the extension of liver pathology[43].

Treatment of hepatitis C is usually consists of a combination of IFN and ribavirin. As Ribavirin is metabolized in the kidney, it should not be used in patients with a creatinine clearance less than 50. INF can be used in patients before transplantation to decrease viral load and it decreases the liver morbidity[44]. Although INF use is associated with acute graft rejection as studied in treatment of CMV infections in post renal transplant recipients[45], recent studies in post liver transplant recipients have not demonstrated significant rejection. Therefore, INF can be considered for treatment of

Table 3 Treatment of viral infections kidney transplant recipients

CMV	CMV load copy no < 500 - below quantifiable level - no action
	CMV load copy no 500-3000 - active CMV infection - repeat CMV in 1 week, consider treatment if clinically indicated
	CMV load copy no > 3000 - Active CMV infection - commence pre-emptive treatment
	Intravenous ganciclovir or oral valganciclovir
EBV	Immunosuppressive drug reduction
	Ganciclovir and valganciclovir have antiviral impact against EBV
BKPyV	Immunosuppressive drug reduction
	No specific antiviral therapy
HSV	Acyclovir
	Intravenous or oral
VZV	Intravenous acyclovir, while less severe infection can be treated with oral acyclovir
Hepatitis B & C	Immunosuppressive drug reduction
	Hepatitis B - Lamivudine
	Hepatitis C - IFN and ribavirin
Respiratory viruses	Reduce immunosuppressive drugs
	Supportive care and, in some cases, the use of antivirals

CMV: Cytomegalovirus, EBV: Epstein-Barr virus, BKPyV: Human BK polyomavirus, HSV: Herpes simplex viruses, VZV: Varicella zoster virus.

Hepatitis C in the renal transplant recipients[46].

PREVENTION

Cytomegalovirus infection is prevented mainly two strategies that involve either universal therapy or preemptive therapy (Table 4). Antiviral treatment is administered continuously during the peak of the post-transplantation immunosuppression period in universal therapy whilst they are administered according to thresholds of CMV anti-genemia or DNA titers in pre-emptive therapy[25]. Either intravenous ganciclovir or oral valganciclovir is used in prevention of cytomegalovirus infections in the transplant recipient. Universal therapy is generally associated with higher prevalence of side-effects and increased costs whereas preemptive therapy needs facilities for timely monitoring of viral kinetics to guide preventive treatment. Serostatus of the donor and the recipient is a key factor in determining the correct preventative approach[47]. High risk D+/R- kidney transplant recipients benefit from universal therapy with a longer 6-mo course of oral valganciclovir given at preventive doses [Dose (mg) = (7 × BSA × eGFR) once a day]. Universal therapy is also indicated for those R+ patients who were treated with lymphocyte depleting immunosuppressive therapy and a course with oral valganciclovir is recommended up to a duration of 6-mo. Preemptive therapy is mainly indicated for R+ recipients with weekly monitoring of the viral load to guide therapy and a 12-wk course is recommended for those who successfully respond. The routine use of preventative therapy is not recommended for D-/R- renal transplant recipients. D-/R- patients should be given either leukodepleted or CMV negative blood products to prevent CMV acquired through blood products.

Most important preventive measure against development of post-transplantation lymphoproliferative disorder in patients with increasing EBV viral loads is reduction in the immunosuppression in a step-wise manner. It is recommended that calcineurin inhibitors are maintained at an acceptable lower level to reduce the risk of development of PTLD [48]. However, it is critical that graft function is monitored to detect early graft rejection early during the phase of reduction in immunosuppression. Although some experts advocate treating patients with high viral loads with either ganciclovir or valganciclovir, the evidence base for this practice is not strong. Similarly, there is a wide variation in the practice of treating patients with higher EBV viral loads with rituximab in those who do not respond to reduction in immunosuppression alone[49].

Prevention of Polyomavirus BK associated nephropathy is achieved by early detection of viraemia and modification of immunosuppressive treatment. As children manifest nephropathy earlier than adults more frequent monitoring for viraemia is indicated in children following the period immediately following the kidney transplantation[35].

Intravenous palivizumab (an RSV-specific monoclonal antibody) prevents progression of respiratory infections in children with suppressed immunity[50]. Vaccination of patients is also important in preventing them from acquiring opportunistic viral and bacterial respiratory infections[51].

Table 4 Prevention of viral infections kidney transplant recipients

CMV	Valganciclovir Universal prophylaxis - Dose (mg) = $(7 \times \text{BSA} \times \text{eGFR})$ once a day Preemptive therapy - Dose (mg) = $(7 \times \text{BSA} \times \text{eGFR})$ bd
EBV	EBV viral load surveillance and preemptive therapy for EBV mismatched patients
BKPyV	BK viral load monitoring and early identification of BK viremia
HSV	Avoidance of visitors or health professionals who have HSV signs and symptoms
VZV	Avoidance of visitors or health professionals who have VZV signs and symptoms. Vaccination including family members
Hepatitis B & C	Hepatitis B vaccination and immunity verified with Hepatitis B surface antibody screening following completion of the vaccination series
Respiratory viruses	Avoidance of other individuals who have signs or symptoms of infection, hand hygiene, and use of droplet precautions for those suspected of having infection

CMV: Cytomegalovirus; EBV: Epstein-Barr virus; BKPyV: Human BK polyomavirus; HSV: Herpes simplex viruses; VZV: Varicella zoster virus.

Hepatitis B infection can be prevented by vaccination of all nonimmune patients with end stage renal disease with hepatitis B vaccine series. The post vaccine immunity should be verified with hepatitis B surface antibody levels. If antibody levels are below the recommended immunity level, a booster dose of vaccine is indicated. Screening of hepatitis C in children with end stage renal failure may be confounded by the reduced serological sensitivity in this cohort. Thus, all hepatitis C seronegative transplant recipients with deranged transaminases and/or risk factors for hepatitis C should have quantification of viral load[52].

More frequent monitoring and preemptive treatment have resulted in better control of viral infections while reducing graft rejection due to undesirable reductions in immunosuppressive therapy. Monitoring of the viral loads according to the institutional protocol and evaluation of the immune status of the individual patient is therefore, crucial improving the outcomes of the transplant recipient children.

CONCLUSION

Paediatric renal transplant recipients are at high risk of acquiring virus-related complications due to immunological immaturity and the enhanced alloreactivity risk that led to maintenance of high immunosuppressive regimes. Herpes simplex virus, varicella zoster virus, Epstein-Barr virus, cytomegalovirus, hepatitis B & C viruses, BK polyomavirus, and adenovirus are common in this cohort. These viruses can cause severe systemic diseases or allograft dysfunction affecting the clinical outcome.

More frequent monitoring and preemptive treatment have resulted in better control of viral infections while reducing graft rejection due to undesirable reductions in immunosuppressive therapy. Recent advances in technology and antiviral therapy with precise treatment in the immunocompromised host has result in significant impact on outcome.

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