**Name of Journal:** *World Journal of Transplantation*

**Manuscript NO:** 89978

**Manuscript Type:** MINIREVIEWS

**Management strategies for common viral infections in pediatric renal transplant recipients**

Ranawaka R *et al*. Viral infections in renal transplant recipients

Randula Ranawaka, Kavinda Dayasiri, Erandima Sandamali, Manoji Gamage

**Randula Ranawaka,** Department of Paediatrics, Faculty of Medicine, University of Colombo and Lady Ridgeway Hospital for Children, Colombo 0094, Sri Lanka

**Kavinda Dayasiri,** Department of Paediatrics, Facullty of Medicine, University of Kelaniya, Ragama 0094, Sri Lanka

**Erandima Sandamali,** Department of Nursing, Faculty of Allied Health Sciences, University of Ruhuna, Galle 0094, Sri Lanka

**Manoji Gamage,** Division ofNutrition, Ministry of Health, Colombo 0094, Sri Lanka

**Author contributions:** Ranawaka R, Dayasiri K, Sandamali E, Gamage M performed literature survey; Ranawaka R, Dayasiri K, Sandamali E, Gamage M wrote the manuscript; Ranawaka R edited the final version of the manuscript; all authors read and approved the final version of the manuscript.

**Corresponding author: Randula Ranawaka, MBBS, MD, Chief Physician, Professor, Senior Researcher,** Department of Paediatrics, Faculty of Medicine, University of Colombo and Lady Ridgeway Hospital for Children, Kynsey Road, Colombo 0094, Sri Lanka. randula@pdt.cmb.ac.lk

**Received:** November 20, 2023

**Revised:** December 19, 2023

**Accepted:** January 4, 2024

**Published online:**

**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

Ranawaka R, Dayasiri K, Sandamali E, Gamage M. Management strategies for common viral infections in pediatric renal transplant recipients. *World J Transplant* 2024; In press

**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.

**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 viruria precedes viraemia by several weeks due to predominant proliferation of the virus in the urothelium, the correlation with viruria 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 viruria has a higher negative predictive value and viruria may be used as a first line screening test in suspecting early nephropathy[29]. However, given the limited specificity of viruria, 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.

**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 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 antigenemia 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 thorough 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].

Hepatitis B infection can be prevented by vaccination of all nonimmune patients with ends 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 ends 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.

**ACKNOWLEDGEMENTS**

All authors sincerely thank Dr. Dominic Kelly of the University of Oxford for conducting English language editing of this manuscript.

**REFERENCES**

1 **Helmuth ME**, Liu Q, Turenne MN, Park JM, Oguntimein M, Dutcher SK, Balkrishnan R, Sharma P, Zee J, Leichtman AB, Smith AR. Secular Trends in the Cost of Immunosuppressants after Solid Organ Transplantation in the United States. *Clin J Am Soc Nephrol* 2019; **14**: 421-430 [PMID: 30819667 DOI: 10.2215/CJN.10590918]

2 **Schnitzler MA**, Skeans MA, Axelrod DA, Lentine KL, Tuttle-Newhall JE, Snyder JJ, Israni AK, Kasiske BL. OPTN/SRTR 2013 Annual Data Report: economics. *Am J Transplant* 2015; **15 Suppl 2**: 1-24 [PMID: 25626348 DOI: 10.1111/ajt.13201]

3 **Fishman JA**, Rubin RH. Infection in organ-transplant recipients. *N Engl J Med* 1998; **338**: 1741-1751 [PMID: 9624195 DOI: 10.1056/NEJM199806113382407]

4 **Comoli P**, Ginevri F. Monitoring and managing viral infections in pediatric renal transplant recipients. *Pediatr Nephrol* 2012; **27**: 705-717 [PMID: 21359619 DOI: 10.1007/s00467-011-1812-2]

5 **Silva JT**, Fernández-Ruiz M, Aguado JM. Prevention and therapy of viral infections in patients with solid organ transplantation. *Enferm Infecc Microbiol Clin (Engl Ed)* 2021; **39**: 87-97 [PMID: 32143894 DOI: 10.1016/j.eimc.2020.01.021]

6 **Griffiths P**, Baraniak I, Reeves M. The pathogenesis of human cytomegalovirus. *J Pathol* 2015; **235**: 288-297 [PMID: 25205255 DOI: 10.1002/path.4437]

7 **Haidar G**, Singh N. Viral infections in solid organ transplant recipients: novel updates and a review of the classics. *Curr Opin Infect Dis* 2017; **30**: 579-588 [PMID: 28984642 DOI: 10.1097/QCO.0000000000000409]

8 **Hill P**, Cross NB, Barnett AN, Palmer SC, Webster AC. Polyclonal and monoclonal antibodies for induction therapy in kidney transplant recipients. *Cochrane Database Syst Rev* 2017; **1**: CD004759 [PMID: 28073178 DOI: 10.1002/14651858.CD004759.pub2]

9 **Ramanan P**, Razonable RR. Cytomegalovirus infections in solid organ transplantation: a review. *Infect Chemother* 2013; **45**: 260-271 [PMID: 24396627 DOI: 10.3947/ic.2013.45.3.260]

10 **Ljungman P**, Boeckh M, Hirsch HH, Josephson F, Lundgren J, Nichols G, Pikis A, Razonable RR, Miller V, Griffiths PD; Disease Definitions Working Group of the Cytomegalovirus Drug Development Forum. Definitions of Cytomegalovirus Infection and Disease in Transplant Patients for Use in Clinical Trials. *Clin Infect Dis* 2017; **64**: 87-91 [PMID: 27682069 DOI: 10.1093/cid/ciw668]

11 **Gavalda J**, Len O, San Juan R, Aguado JM, Fortun J, Lumbreras C, Moreno A, Munoz P, Blanes M, Ramos A, Rufi G, Gurgui M, Torre-Cisneros J, Montejo M, Cuenca-Estrella M, Rodriguez-Tudela JL, Pahissa A; RESITRA (Spanish Network for Research on Infection in Transplantation). Risk factors for invasive aspergillosis in solid-organ transplant recipients: a case-control study. *Clin Infect Dis* 2005; **41**: 52-59 [PMID: 15937763 DOI: 10.1086/430602]

12 **Fernàndez-Sabé N**, Cervera C, López-Medrano F, Llano M, Sáez E, Len O, Fortún J, Blanes M, Laporta R, Torre-Cisneros J, Gavaldà J, Muñoz P, Fariñas MC, María Aguado J, Moreno A, Carratalà J. Risk factors, clinical features, and outcomes of listeriosis in solid-organ transplant recipients: a matched case-control study. *Clin Infect Dis* 2009; **49**: 1153-1159 [PMID: 19751149 DOI: 10.1086/605637]

13 **Nijland ML**, Kersten MJ, Pals ST, Bemelman FJ, Ten Berge IJ. Epstein-Barr Virus-Positive Posttransplant Lymphoproliferative Disease After Solid Organ Transplantation: Pathogenesis, Clinical Manifestations, Diagnosis, and Management. *Transplant Direct* 2016; **2**: e48 [PMID: 27500242 DOI: 10.1097/TXD.0000000000000557]

14 **Dierickx D**, Habermann TM. Post-Transplantation Lymphoproliferative Disorders in Adults. *N Engl J Med* 2018; **378**: 549-562 [PMID: 29414277 DOI: 10.1056/NEJMra1702693]

15 **Hirsch HH**, Brennan DC, Drachenberg CB, Ginevri F, Gordon J, Limaye AP, Mihatsch MJ, Nickeleit V, Ramos E, Randhawa P, Shapiro R, Steiger J, Suthanthiran M, Trofe J. Polyomavirus-associated nephropathy in renal transplantation: interdisciplinary analyses and recommendations. *Transplantation* 2005; **79**: 1277-1286 [PMID: 15912088 DOI: 10.1097/01.TP.0000156165.83160.09]

16 **Funk GA**, Steiger J, Hirsch HH. Rapid dynamics of polyomavirus type BK in renal transplant recipients. *J Infect Dis* 2006; **193**: 80-87 [PMID: 16323135 DOI: 10.1086/498530]

17 **Ginevri F,** Hirsch HH. Polyomavirus-associated nephropa-thy. In: Molony DA, Craig JC (eds) Evidence-Based Nephrology. John Wiley & Sons, London, 2008 [DOI: 10.1002/9781444303391.ch26]

18 **Abdel Massih RC**, Razonable RR. Human herpesvirus 6 infections after liver transplantation. *World J Gastroenterol* 2009; **15**: 2561-2569 [PMID: 19496184 DOI: 10.3748/wjg.15.2561]

19 **Kim YJ**, Boeckh M, Englund JA. Community respiratory virus infections in immunocompromised patients: hematopoietic stem cell and solid organ transplant recipients, and individuals with human immunodeficiency virus infection. *Semin Respir Crit Care Med* 2007; **28**: 222-242 [PMID: 17458776 DOI: 10.1055/s-2007-976494]

20 **Blanchard SS**, Gerrek M, Siegel C, Czinn SJ. Significant morbidity associated with RSV infection in immunosuppressed children following liver transplantation: case report and discussion regarding need of routine prophylaxis. *Pediatr Transplant* 2006; **10**: 826-829 [PMID: 17032430 DOI: 10.1111/j.1399-3046.2006.00583.x]

21 **Martin-Gandul C**, Stampf S, Héquet D, Mueller NJ, Cusini A, van Delden C, Khanna N, Boggian K, Hirzel C, Soccal P, Hirsch HH, Pascual M, Meylan P, Manuel O; Swiss Transplant Cohort Study (STCS). Preventive Strategies Against Cytomegalovirus and Incidence of α-Herpesvirus Infections in Solid Organ Transplant Recipients: A Nationwide Cohort Study. *Am J Transplant* 2017; **17**: 1813-1822 [PMID: 28039960 DOI: 10.1111/ajt.14192]

22 **Fernández-Ruiz M**, Origüen J, Lora D, López-Medrano F, González E, Polanco N, San Juan R, Ruiz-Merlo T, Parra P, Andrés A, Aguado JM. Herpes zoster in kidney transplant recipients: protective effect of anti-cytomegalovirus prophylaxis and natural killer cell count. A single-center cohort study. *Transpl Int* 2018; **31**: 187-197 [PMID: 28940695 DOI: 10.1111/tri.13076]

23 **Marinaki S**, Kolovou K, Sakellariou S, Boletis JN, Delladetsima IK. Hepatitis B in renal transplant patients. *World J Hepatol* 2017; **9**: 1054-1063 [PMID: 28951777 DOI: 10.4254/wjh.v9.i25.1054]

24 **Fornairon S**, Pol S, Legendre C, Carnot F, Mamzer-Bruneel MF, Brechot C, Kreis H. The long-term virologic and pathologic impact of renal transplantation on chronic hepatitis B virus infection. *Transplantation* 1996; **62**: 297-299 [PMID: 8755832 DOI: 10.1097/00007890-199607270-00025]

25 **Torre-Cisneros J**, Aguado JM, Caston JJ, Almenar L, Alonso A, Cantisán S, Carratalá J, Cervera C, Cordero E, Fariñas MC, Fernández-Ruiz M, Fortún J, Frauca E, Gavaldá J, Hernández D, Herrero I, Len O, Lopez-Medrano F, Manito N, Marcos MA, Martín-Dávila P, Monforte V, Montejo M, Moreno A, Muñoz P, Navarro D, Pérez-Romero P, Rodriguez-Bernot A, Rumbao J, San Juan R, Vaquero JM, Vidal E; Spanish Society of Transplantation (SET); Group for Study of Infection in Transplantation of the Spanish Society of Infectious Diseases and Clinical Microbiology (GESITRA-SEIMC); Spanish Network for Research in Infectious Diseases (REIPI). Management of cytomegalovirus infection in solid organ transplant recipients: SET/GESITRA-SEIMC/REIPI recommendations. *Transplant Rev (Orlando)* 2016; **30**: 119-143 [PMID: 27132815 DOI: 10.1016/j.trre.2016.04.001]

26 **Allen UD**, Preiksaitis JK; AST Infectious Diseases Community of Practice. Post-transplant lymphoproliferative disorders, Epstein-Barr virus infection, and disease in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant* 2019; **33**: e13652 [PMID: 31230381 DOI: 10.1111/ctr.13652]

27 **Drachenberg CB**, Papadimitriou JC, Hirsch HH, Wali R, Crowder C, Nogueira J, Cangro CB, Mendley S, Mian A, Ramos E. Histological patterns of polyomavirus nephropathy: correlation with graft outcome and viral load. *Am J Transplant* 2004; **4**: 2082-2092 [PMID: 15575913 DOI: 10.1046/j.1600-6143.2004.00603.x]

28 **Hirsch HH**, Randhawa P; AST Infectious Diseases Community of Practice. BK virus in solid organ transplant recipients. *Am J Transplant* 2009; **9 Suppl 4**: S136-S146 [PMID: 20070673 DOI: 10.1111/j.1600-6143.2009.02904.x]

29 **Vats A**, Shapiro R, Singh Randhawa P, Scantlebury V, Tuzuner A, Saxena M, Moritz ML, Beattie TJ, Gonwa T, Green MD, Ellis D. Quantitative viral load monitoring and cidofovir therapy for the management of BK virus-associated nephropathy in children and adults. *Transplantation* 2003; **75**: 105-112 [PMID: 12544881 DOI: 10.1097/00007890-200301150-00020]

30 **Gupta M**, Diaz-Mitoma F, Feber J, Shaw L, Forget C, Filler G. Tissue HHV6 and 7 determination in pediatric solid organ recipients--a pilot study. *Pediatr Transplant* 2003; **7**: 458-463 [PMID: 14870894 DOI: 10.1046/j.1399-3046.2003.00099.x]

31 **Koval CE**. Prevention and Treatment of Cytomegalovirus Infections in Solid Organ Transplant Recipients. *Infect Dis Clin North Am* 2018; **32**: 581-597 [PMID: 30146024 DOI: 10.1016/j.idc.2018.04.008]

32 **Tedesco-Silva H**, Felipe C, Ferreira A, Cristelli M, Oliveira N, Sandes-Freitas T, Aguiar W, Campos E, Gerbase-DeLima M, Franco M, Medina-Pestana J. Reduced Incidence of Cytomegalovirus Infection in Kidney Transplant Recipients Receiving Everolimus and Reduced Tacrolimus Doses. *Am J Transplant* 2015; **15**: 2655-2664 [PMID: 25988935 DOI: 10.1111/ajt.13327]

33 **Razonable RR**, Humar A. Cytomegalovirus in solid organ transplant recipients-Guidelines of the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant* 2019; **33**: e13512 [PMID: 30817026 DOI: 10.1111/ctr.13512]

34 **Parker A**, Bowles K, Bradley JA, Emery V, Featherstone C, Gupte G, Marcus R, Parameshwar J, Ramsay A, Newstead C; Haemato-oncology Task Force of the British Committee for Standards in Haematology and British Transplantation Society. Management of post-transplant lymphoproliferative disorder in adult solid organ transplant recipients - BCSH and BTS Guidelines. *Br J Haematol* 2010; **149**: 693-705 [PMID: 20408848 DOI: 10.1111/j.1365-2141.2010.08160.x]

35 **Acott PD**, Hirsch HH. BK virus infection, replication, and diseases in pediatric kidney transplantation. *Pediatr Nephrol* 2007; **22**: 1243-1250 [PMID: 17377822 DOI: 10.1007/s00467-007-0462-x]

36 **Ginevri F**, Azzi A, Hirsch HH, Basso S, Fontana I, Cioni M, Bodaghi S, Salotti V, Rinieri A, Botti G, Perfumo F, Locatelli F, Comoli P. Prospective monitoring of polyomavirus BK replication and impact of pre-emptive intervention in pediatric kidney recipients. *Am J Transplant* 2007; **7**: 2727-2735 [PMID: 17908275 DOI: 10.1111/j.1600-6143.2007.01984.x]

37 **Saad ER**, Bresnahan BA, Cohen EP, Lu N, Orentas RJ, Vasudev B, Hariharan S. Successful treatment of BK viremia using reduction in immunosuppression without antiviral therapy. *Transplantation* 2008; **85**: 850-854 [PMID: 18360267 DOI: 10.1097/TP.0b013e318166cba8]

38 **Montejo M**, Ramon Fernandez J, Testillano M, Valdivieso A, Aguirrebengoa K, Varas C, Olaizola A, De Urbina JO. Encephalitis caused by human herpesvirus-6 in a liver transplant recipient. *Eur Neurol* 2002; **48**: 234-235 [PMID: 12422078 DOI: 10.1159/000066172]

39 **Takahashi K,** Suzuki M, Iwata Y, Shigeta S, Yamanishi K, De Clercq E. Selective activity of various nucleoside and nucleotide analogues against human herpesvirus 6 and 7. *Antivir Chem Chemother* 1997; **8**:24-31 [DOI: 10.1177/095632029700800102]

40 **McCurdy LH**, Milstone A, Dummer S. Clinical features and outcomes of paramyxoviral infection in lung transplant recipients treated with ribavirin. *J Heart Lung Transplant* 2003; **22**: 745-753 [PMID: 12873542 DOI: 10.1016/S1053-2498(02)00569-7]

41 **Pelaez A**, Lyon GM, Force SD, Ramirez AM, Neujahr DC, Foster M, Naik PM, Gal AA, Mitchell PO, Lawrence EC. Efficacy of oral ribavirin in lung transplant patients with respiratory syncytial virus lower respiratory tract infection. *J Heart Lung Transplant* 2009; **28**: 67-71 [PMID: 19134533 DOI: 10.1016/j.healun.2008.10.008]

42 **Carter BA**, Karpen SJ, Quiros-Tejeira RE, Chang IF, Clark BS, Demmler GJ, Heslop HE, Scott JD, Seu P, Goss JA. Intravenous Cidofovir therapy for disseminated adenovirus in a pediatric liver transplant recipient. *Transplantation* 2002; **74**: 1050-1052 [PMID: 12394854 DOI: 10.1097/00007890-200210150-00027]

43 **Green M,** Avery R, Preiksaitis J. Guidelines for the prevention and management of infectious complications of solid organ transplantation. *Am J Transplant* 2004; **4:** 10-17, 57-109, 160-163 [DOI: 10.1111/j.1600-6135.2004.00737.x]

44 **Casanovas Taltavull T**, Baliellas C, Sesé E, Iborra MJ, Benasco C, Andrés E, González MT, Gil-Vernet S, Casanova A, Casais LA. Interferon may be useful in hemodialysis patients with hepatitis C virus chronic infection who are candidates for kidney transplant. *Transplant Proc* 1995; **27**: 2229-2230 [PMID: 7652784]

45 **Kramer P,** ten Kate F, Bijnen A, Jeekel J, Weimar W: The pathology of interferon-induced allograft lesions. Transplant Proc 17: 58-60, 1985

46 **Shu KH**, Lan JL, Wu MJ, Cheng CH, Chen CH, Lee WC, Chang HR, Lian JD. Ultralow-dose alpha-interferon plus ribavirin for the treatment of active hepatitis C in renal transplant recipients. *Transplantation* 2004; **77**: 1894-1896 [PMID: 15223909 DOI: 10.1097/01.TP.0000131151.07818.D7]

47 **Moghadamnia M**, Eshaghi H, Alimadadi H, Dashti-Khavidaki S. A quick algorithmic review on management of viral infectious diseases in pediatric solid organ transplant recipients. *Front Pediatr* 2023; **11**: 1252495 [PMID: 37732007 DOI: 10.3389/fped.2023.1252495]

48 **San-Juan R**, Comoli P, Caillard S, Moulin B, Hirsch HH, Meylan P; ESCMID Study Group of Infection in Compromised Hosts. Epstein-Barr virus-related post-transplant lymphoproliferative disorder in solid organ transplant recipients. *Clin Microbiol Infect* 2014; **20 Suppl 7**: 109-118 [PMID: 24475976 DOI: 10.1111/1469-0691.12534]

49 **San-Juan R**, Manuel O, Hirsch HH, Fernández-Ruiz M, López-Medrano F, Comoli P, Caillard S, Grossi P, Aguado JM; ESGICH PTLD Survey Study Group,; European Study Group of Infections in Compromised Hosts (ESGICH) from the European Society of Microbiology and Infectious Diseases (ESCMID). Current preventive strategies and management of Epstein-Barr virus-related post-transplant lymphoproliferative disease in solid organ transplantation in Europe. Results of the ESGICH Questionnaire-based Cross-sectional Survey. *Clin Microbiol Infect* 2015; **21**: 604.e1-604.e9 [PMID: 25686696 DOI: 10.1016/j.cmi.2015.02.002]

50 **Thomas NJ**, Hollenbeak CS, Ceneviva GD, Geskey JM, Young MJ. Palivizumab prophylaxis to prevent respiratory syncytial virus mortality after pediatric bone marrow transplantation: a decision analysis model. *J Pediatr Hematol Oncol* 2007; **29**: 227-232 [PMID: 17414564 DOI: 10.1097/MPH.0b013e3180437ded]

51 **Scharpé J**, Evenepoel P, Maes B, Bammens B, Claes K, Osterhaus AD, Vanrenterghem Y, Peetermans WE. Influenza vaccination is efficacious and safe in renal transplant recipients. *Am J Transplant* 2008; **8**: 332-337 [PMID: 18162092 DOI: 10.1111/j.1600-6143.2007.02066.x]

52 Recommendations for preventing transmission of infections among chronic hemodialysis patients. *MMWR Recomm Rep* 2001; **50**: 1-43 [PMID: 11349873]

**Footnotes**

**Conflict-of-interest statement:** All the authors declare that they have no conflict of interest.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Corresponding Author's Membership in Professional Societies:** International Society of Nephrology, 201267; Sri Lankan Society of Nephrology.

**Peer-review started:** November 20, 2023

**First decision:** December 11, 2023

**Article in press:**

**Specialty type:** Transplantation

**Country/Territory of origin:** Sri Lanka

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Zhang XN, China **S-Editor:** Liu JH **L-Editor:** A **P-Editor:**

**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.

**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.

**Table 4 Prevention of viral infections kidney transplant recipients**

|  |  |
| --- | --- |
| CMV | Valganciclovir |
| Universal prophylaxis - Dose (mg) = (7 × BSA × eGFR) once a day |
| Preemptive therapy - Dose (mg) = ( 7 × BSA × 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.