Prevention and Treatment of Polyomavirus-Associated Diseases

8

Joanna Schaenman and Chen Sabrina Tan

8.1 Description of Pathogens

The human polyomaviruses are ubiquitous non-enveloped DNA viruses in the *Orthopolyomavirus* genus and the *Polyomaviridae* family [1]. BKV was first isolated from the urine of a kidney transplant recipient with the initials of "BK," who presented with ureteric stenosis and obstruction [2]. JCV was initially isolated from the brain of the lymphoma patient with the initials of "JC," who had multiple areas of demyelination in the brain.

BKV and JCV are small non-enveloped double-stranded DNA virus with approximately 5 Kb of genome, which encodes the capsid proteins—VP1, 2, and 3, large T antigen, small T antigen, and agnoprotein. The genome also contains a ~200 bp noncoding region which serves as binding sites for transcriptional factors. Due to lack of viral DNA polymerase, BKV and JCV use the host machinery for viral replication. Multiple genotypes of each virus have been identified based on nucleotide differences in VP1; the distributions of specific genotypes are used as markers to trace human migrations throughout the world [3].

J. Schaenman (✉)
Division of Infectious Diseases, Department of Medicine, David Geffen School of Medicine at the University of California Los Angeles, Los Angeles, CA, USA
e-mail: JSchaenman@mednet.ucla.edu

C. Sabrina Tan
Department of Medicine, Division of Infectious Diseases, Center for Virology and Vaccines Research, Harvard Medical School, Boston, MA, USA
e-mail: CTan@bidmc.harvard.edu

8.2 BKV

8.2.1 Definitions and Epidemiology

Asymptomatic primary infection with BKV most likely occurs in childhood. Seroprevalence worldwide is 65–90% and increases with age [4]. After primary infection, BKV resides in the kidney tubular epithelial cells. Occasional viral replication occurs as BKV is detected in the urine of up to 10% of healthy individuals. BKV viuria is not associated with any disease in healthy individuals. Active BKV replication is associated with diseases in immunosuppressed individuals, specifically, those with kidney transplants and those with hematopoietic stem cell transplant. After kidney transplant, BKV can be detected in urine (~30%) and blood (10–20%) of the recipients. Patients with viremia are at risk of developing BKV-associated nephropathy (BKVN), which occurs in 1–10% of kidney transplant recipients [5] (Table 8.1). Up to about half of those with diagnosed

Table 8.1 BKV definitions

Term	Definition	Clinical implication/action suggested
BK viuria	Detectable BKV from urine by PCR testing	Predictive of BK viremia, suggest check BKV in plasma
BK viremia	Detectable BKV from plasma	• High viral load is predictive of development of BKVAN • Threshold for clinical response not well defined • Monitor renal function • Consider reduction in immunosuppression and/or biopsy
BKV-associated nephropathy (BKN)	Kidney dysfunction in association with detection of BKV by PCR in blood in (presumptive) or detected by biopsy (proven). Grading by Banff criteria [16]	Reduce immunosuppression (see Fig. 8.1)
BKN: Class 1	• ≤1% of all tubules/ducts with viral replication • Interstitial fibrosis in up to 25% of cortical area (mild interstitial fibrosis)	As above
BKN: Class 2	Either • ≤1% of all tubules/ducts with viral replication with interstitial fibrosis in ≤25% of cortical area (moderate to severe interstitial fibrosis) • or >1% to ≤10% of all tubules/ducts with viral replication with any level of interstitial fibrosis • or >10% of all tubules/ducts with viral replication with mild interstitial fibrosis	As above
BKN: Class 3	• >10% of all tubules/ducts with viral replication with mild interstitial fibrosis with moderate to severe interstitial fibrosis	As above

nephropathy will sustain graft loss. The majority of the BKVN cases occurs during the first year post transplant [6]; risks of developing BKVN include male sex, age, ureteric stents, donor seropositivity, increased levels of immunosuppression, and use of tacrolimus [7, 8]. Evidences show that most viral strains are from the donor [9, 10]. BKV viuria and viremia can occur in transplant recipients of other solid organs, such as the heart, liver, and lung, but at low incidences of 20% and 3%, respectively. These patients rarely progress to nephropathy absent a transplanted kidney [11]. Persistent viremia may also increase the risk of developing de novo donor-specific antibodies [12].

The detection of BKV in the urine has also been associated with genitourinary tumors [13].

8.2.2   Screening

BKV screening is performed post kidney transplant to reduce nephropathy and prevent graft loss. AST and KDIGO recommended systematic screening for BKV by PCR detection in kidney transplant recipients: monthly for the first 6 months after transplant and then every 3 months thereafter until 2 years [14, 15] (Fig. 8.1). Some centers screen urine for decoy cells, although this approach is less sensitive compared with PCR detection. Detection of the virus in urine is in of itself not associated with nephropathy. In those patients who go on to develop BK viremia, detection of virus in the urine usually precedes viremia by 4–12 weeks. Although specific virus quantity thresholds have not been prospectively developed, a blood viral load >10,000 copies/ml is highly associated with nephropathy.

8.2.3   Diagnosis

While detection of BKV in blood greater than $4\log_{10}$ copies/ml is presumptive of nephropathy in the kidney, pathological findings in kidney tissues obtained from biopsy are the gold standard in diagnosing BKV-associated nephropathy (BKN, also termed polyomavirus nephropathy (PVN) (Fig. 8.2). Histologically, BKN is categorized into three groups based on the latest Banff Working Group classifications, correlating to both increased creatinine and increased risk of graft loss from 16% to 31% to 50% [16]. Class 1, defined as involvement of ≤1% of all tubules/ducts with viral replication with minimal interstitial fibrosis, represents early-stage disease with favorable outcomes. Class 2 is defined as either minimal viral replication with more severe interstitial fibrosis or >1% to ≤10% of all tubules/ducts with viral replication. Class 3 carries the most severe prognosis and is defined as >10% of all tubules/ducts with viral replication. These classifications provide prognostic information at the time of kidney biopsy [16]. Of note, due to nonuniform involvement of the kidney, kidney biopsy may fail to detect BKN resulting in a false-negative biopsy [14].
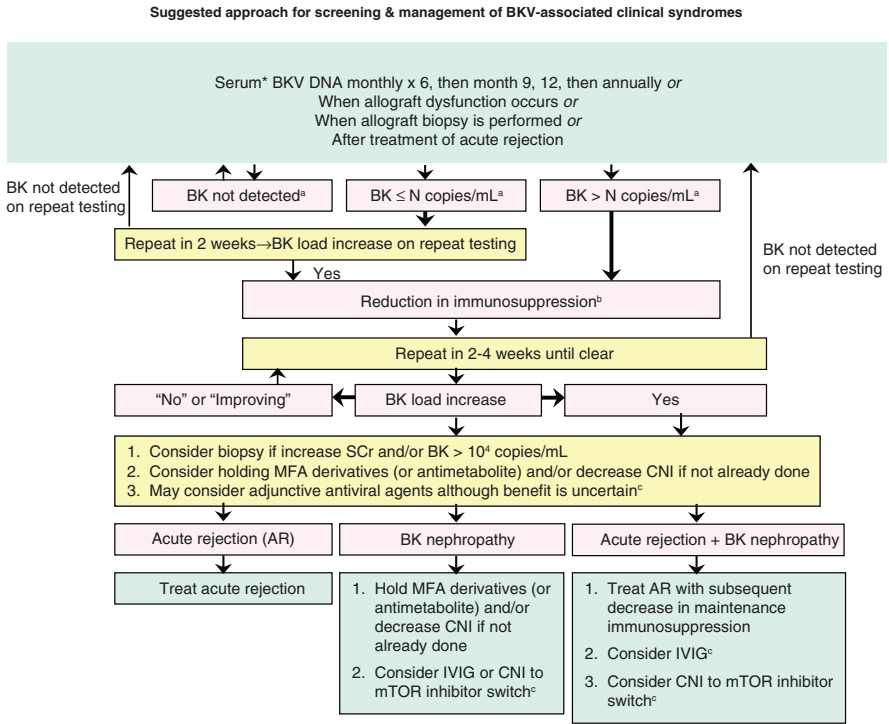
Suggested approach for screening & management of BKV-associated clinical syndromes

Fig. 8.1 BKV screening and management after kidney transplantation. *Alternatively screen with urine BKV PCR; perform serum testing if positive. [a]No standardized PCR assays for BKV are currently available. Cutoff levels for viral detection should be based on PCR assays used at individual institutions. N signifies the threshold established at each institution for BKV serum PCR positivity in copies/ml. [b]Common practice: (1) decrease or hold MFA derivatives (or antimetabolite), (2) decrease (MFA + CNI) by 25–50%, (3) decrease CNI. [c]Evidence-based recommendations are lacking (ongoing clinical trials). May avoid long-term nephrotoxic effect of CNI therapy. Not recommended in patients with baseline significant proteinuria (arbitrarily defined as >500 mg/24 h or at the discretion of the clinician). *SCr* serum creatinine, *MFA* mycophenolate acid, *CNI* calcineurin inhibitor, *AR* acute rejection, *BKN* BK nephropathy, *mTOR* mammalian target of rapamycin, *IVIG* intravenous immunoglobulins, *CSA* cyclosporine. Adapted from Pham PT, Schaenman J, Pham PC. Medical management of the renal transplant recipient: Infections and malignancies. In: Johnson RJ, Feehally J. Comprehensive Clinical Nephrology. Sixth Edition. Elsevier Saunders, Philadelphia, PA

8.2.4 Prevention

Systematic screening for evidence of BKV replication is effective in preventing disease when followed with reduction of immunosuppressants to promote adaptive anti-BKV immune responses [17] (Fig. 8.1). A general approach is to either reduce calcineurin inhibitors 25–50% and mycophenolate by 50% at onset of viremia [14, 15]. Further reduction may be needed with persistent viremia. Switching immunosuppressants to an mTOR inhibitor has been hypothesized and tried, based on the evidence that BKV uses the mTOR pathway for viral replication [18, 19].
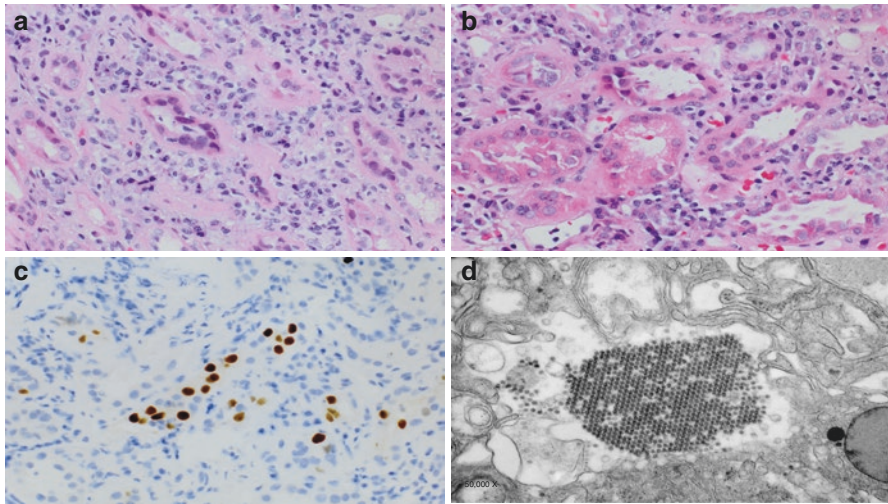
Fig. 8.2 BKN histology. Hematoxylin and eosin stain demonstrating tubular epithelial cells with viral inclusions and interstitial inflammation in (**a**, **b**). SV-40 antibody stain showing BKV-infected cells in (**c**), and electron microscopy image captured the BK virus (**d**). Images **a–c** courtesy of Dr. Fernando Palma-Diaz. (**a**) Hematoxylin and eosin stain, showing tubular epithelial cells some with viral inclusions along with interstitial inflammation. (**b**) Hematoxylin and eosin stain; tubular atrophy and surrounding interstitial inflammation. (**c**) Immunohistochemistry staining for the SV40 antigen demonstrates nuclear staining in infected cells. (**d**) Ultrastructure of BKV-associated nephropathy. Virions are arranged in a paracrystalloid structure within a tubular epithelial cell nucleus.

8.2.5 Treatment

There is no effective antiviral against BKV [20]. The mainstay of treatment is to reduce immunosuppression as discussed above [17, 21]. This is balanced with risk of rejection. The goal of reduction of immunosuppression is to restore adaptive immune responses against BKV. Specifically, BKV-specific T cell with polyfunctionality is crucial in control of viremia [22, 23]. Therefore, there is potential for harnessing adoptive T cells as treatment for BKV [24, 25].

While most patients have prior exposure to BKV and detectable antibodies against the virus, genotype-specific neutralizing antibodies may be required for control of viremia [26]. The BKV-neutralizing antibodies are specific to genotypes and do not cross react. This knowledge supports a potential role for developing broadly neutralizing antibodies against BKV and the use of intravenous infusion of pooled immunoglobulins (IVIG) [27]. Although case reports indicated control of viremia with IVIG [28], a randomized double-blinded clinical trial is underway to determine efficacy of this treatment.

Several potential medications have been studied in treatment of BKV viremia. Leflunomide, a pyrimidine synthesis inhibitor, has been given to kidney transplant recipients with BKV viremia with mixed effect [17, 29–32]. The drug was given in conjunction with reduction in immunosuppression in all cases, and a

meta-analysis comparing drug effect to immunosuppression alone did not show a difference [33]. Based on in vitro demonstration of viral inhibition by DNA gyrase inhibitors, fluoroquinolones have been also tried in the prevention and treatment of BKV infections. Two randomized studies failed to find clinical efficacy of fluoroquinolones in prevention and treatment of BKV viremia [34, 35]. Cidofovir, a nucleotide analogue, showed mixed effect in a non-randomized cohort study and in several case reports [36] but all in conjunction with reduction of immunosuppressants. There was no difference in a meta-analysis of reduction of immunosuppression with cidofovir compared to reduction alone [17]. Brincidofovir, a cidofovir with a lipid tail to enhance transport across the cellular membrane, is an antiviral drug in development that has shown promise as an anti-BK virus agent in cell culture and in case reports [37, 38]. However, efficacy of this drug in treatment of BK virus infection remains to be determined. Switch to mTOR inhibitors may also be of benefit, as suggested by the observed lower incidence of BKV and BKAN in patients receiving sirolimus, and a current randomized controlled trial is underway. T cell transfer of immunity is another promising avenue for treatment currently under development.

8.3 JCV

8.3.1 Definition and Epidemiology

JCV infects 30–90% of the general adult population worldwide, depending on the assay and region [39]. Specific strains of JCV can be used to trace human geographic migrations over time. Primary infection is believed to be asymptomatic and transmitted via urine or fecal to oral route. Although JCV is thought to be latent in the kidney tubular epithelium after primary infection, virus is detected in the urine of up to 30% of healthy individuals, indicating active replication. While viral shedding in the urine by healthy individuals is not associated with any symptom or indicative of any disease, active viral replication in immunocompromised individuals is associated with disease. JCV-associated nephropathy and encephalopathy are rare but have been reported in transplant recipients [40–42]. More prevalent is the JCV replication in the brain, which causes the devastating disease progressive multifocal leukoencephalopathy (PML) in patients with immunosuppression such as HIV, patients with lymphoma, and patients treated with natalizumab—a monoclonal antibody against alpha 4 integrin for multiple sclerosis and Crohn's disease

Table 8.2 Diagnosing PML without histopathology

PML diagnosis	CSF JCV PCR	Clinical characteristics	Radiographic images
Definite	+	+	+
Probable	+	+	−
	+	−	+
Possible	−	+	+

(Table 8.2). PML is a rare disease in transplant recipients, as only 11 cases have been reported in recipients of liver transplant [43, 44]. However, the incidence of PML in heart and/or lung recipients in one center was 1.24 per 1000 post-transplantation person-year, indicating potentially more cases than those reported in literature. In patients with solid organ transplantation, the mean time to detection of first symptom is 27 months, with mean survival of 6.4 months.

8.3.2 Screening

There are no recommended screening tests for transplant patients. Screening for JCV serology has been extensively studied in patients with multiple sclerosis using the STRATIFY JCV index assay. A rise in the antibody index, defined as the ratio between quantities of antibodies in the patient serum to the positive control, can be seen in some patients after prolonged treatment with natalizumab and is associated with increased risk of developing PML [45]. The STRATIFY JCV index has a false-negative rate of up to 2.4% and a poor specificity rate of 40% in patients with high index value. However, this test has not been validated in transplant patients and other immunosuppressed patients. Given the rare incidence of PML in solid organ recipients, screening for JCV by serology titers or PCR detection is currently not recommended.

8.3.3 Diagnosis

The gold standard diagnostic test for PML is brain biopsy demonstrating demyelination, large bizarre astrocytes, and positive immunohistochemical staining with SV40 antibody. Electron microscopy will also show virion-filled cells.

When brain biopsy is contraindicated, presumptive diagnosis is made in clinically appropriate context with CSF analysis, including JCV PCR, and radiographic images [46] (Fig. 8.3). CSF often demonstrates mild protein elevation and some lymphocytic pleocytosis. Glucose is usually within the normal range. PCR for JCV is positive in most cases. Magnetic resonance neuroimaging shows multiple and single areas of demyelination in white matter, irrespective of vascular boundaries. Involvement of gray matters can also be present in some cases. These lesions are T1 hypointense and T2/fluid-attenuating inversion recovery hyperintense. Without PML–IRIS (immune reconstitution inflammatory syndrome), there is no edema or mass effect (Fig. 8.4).

8.3.4 Prevention

Minimize immunosuppression. While risk of developing PML decreases with increased months post transplant, this risk is lifelong, as there are reported cases of patients developing PML years after transplantation.
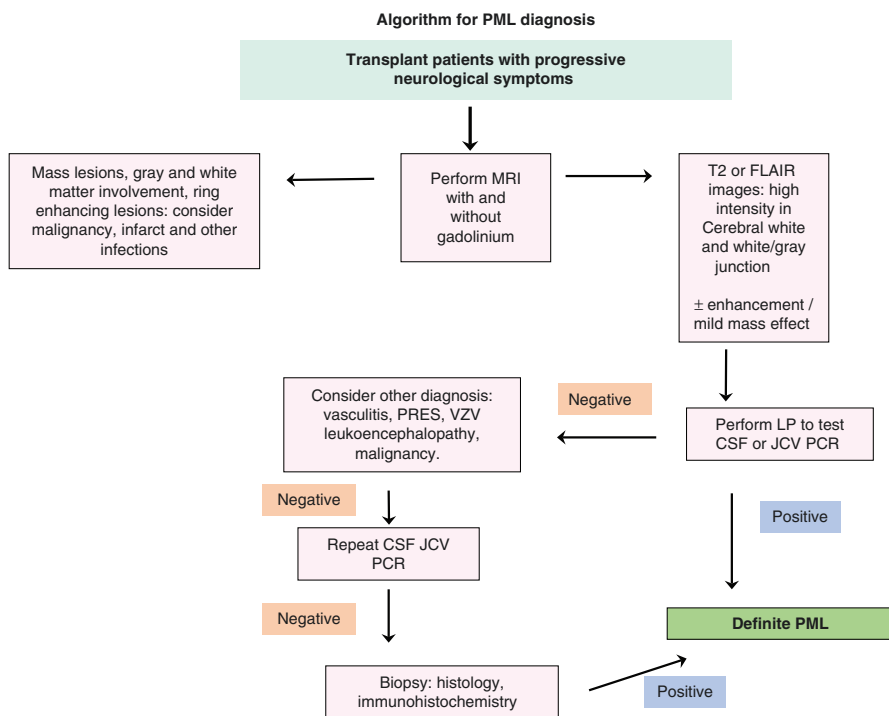
Algorithm for PML diagnosis

**Transplant patients with progressive
neurological symptoms**

Mass lesions, gray and white matter involvement, ring enhancing lesions: consider malignancy, infarct and other infections ← Perform MRI with and without gadolinium → T2 or FLAIR images: high intensity in Cerebral white and white/gray junction

± enhancement / mild mass effect

Consider other diagnosis: vasculitis, PRES, VZV leukoencephalopathy, malignancy. ← Negative ← Perform LP to test CSF or JCV PCR

Negative ↓

Repeat CSF JCV PCR

Positive ↓

Negative ↓

Definite PML

Biopsy: histology, immunohistochemistry ← Positive

Fig. 8.3 PML diagnosis algorithm. *FLAIR* fluid-attenuated inversion recovery, *PRES* posterior reversible encephalopathy syndrome
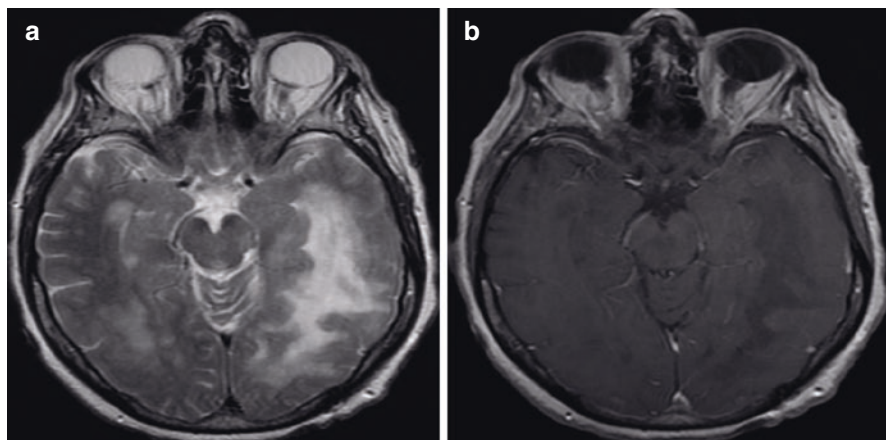

Fig. 8.4 MRI image of PM: brain magnetic resonance images of a 57-year-old woman with progressive multifocal leukoencephalopathy. High-intensity signals were present in the subcortical white matters in the left temporal lobe in T2-weighted image (**a**). These areas are hypointense in T1-weighted image (**b**) and do not enhance with gadolinium

8.3.5 Treatment

There is no effective treatment against JCV. The first step in treatment is to assess the balance of immunosuppression and infection risk of the patient. Reactivation of polyomaviruses is often an indication of overt immunosuppression. Multiple antivirals and even some antibiotics have been tried, including cidofovir, mefloquine, ganciclovir, and leflunomide [47]. Based on the discovery of JCV's use of serotonin receptors to enter cells, mirtazapine, a serotonin receptor antagonist, has also been used as treatment [48]. However, there is no data from clinical studies to support this use. Lastly, there is potential for use of ex vivo stimulated JCV-specific T cells to boost immune response and control viral replication [49]. In PML patients on monoclonal antibody treatments, plasmapheresis can remove the immune-restricting antibody in attempt to revive immune response. However, an IRIS response may follow removal.

Case fatality for PML after transplantation is high at 84% [44]. But the 1-year survival is 56%, comparable to HIV patients on HAART [50].

8.4   Other Human Polyomaviruses

Since 2007, the human polyomavirus family has now expanded to include newly discovered viruses [1]. They are names after places of discovery, KIPyV (Karolinska Institute), WUPyV (Washington University), MWPyV (Malawi), and STLPyV (St. Louis); associated diseases, MCPyV (Merkel Cell) and TSPyV (trichodysplasia spinulosa); and lastly in chronological order of discovery, HPyV6 (human polyomavirus), HPyV7, HPyV9, HPyV12, and HPyV13. Known diseases associated with these viruses are Merkel cell carcinoma caused by MCPyV in immunocompromised patients, trichodysplasia spinulosa—a rare follicular disease caused by TSPyV in pediatric heart transplant recipients—and pruritic rash in lung transplant recipient caused by HPyV7 [51]. While KI and WU have been detected in the respiratory secretions in non-immunocompromised children, there are new reports of KIPyV association with respiratory symptoms in transplant recipients [52, 53].

General Approach General algorithmic approach to identifying and diagnosing focus of topic (introduced above) (Figs. 8.1 and 8.3).

References

1. Johne R, Buck CB, Allander T, Atwood WJ, Garcea RL, Imperiale MJ, Major EO, Ramqvist T, Norkin LC. Taxonomical developments in the family polyomaviridae. Arch Virol. 2011;156(9):1627–34. https://doi.org/10.1007/s00705-011-1008-x.
2. Gardner SD, Field AM, Coleman DV, Hulme B. New human papovavirus (B.K.) isolated from urine after renal transplantation. Lancet. 1971;1(7712):1253–7.

3. Yogo Y, Sugimoto C, Zhong S, Homma Y. Evolution of the BK polyomavirus: epidemiological, anthropological and clinical implications. Rev Med Virol. 2009;19(4):185–99. https://doi.org/10.1002/rmv.613.

4. Kean JM, Rao S, Wang M, Garcea RL. Seroepidemiology of human polyomaviruses. PLoS Pathog. 2009;5(3):e1000363. https://doi.org/10.1371/journal.ppat.1000363.

5. Hirsch HH, Knowles W, Dickenmann M, Passweg J, Klimkait T, Mihatsch MJ, Steiger J. Prospective study of polyomavirus type BK replication and nephropathy in renal-transplant recipients. N Engl J Med. 2002;347(7):488–96. https://doi.org/10.1056/NEJMoa020439.

6. 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(10):1277–86.

7. Hirsch HH, Vincenti F, Friman S, Tuncer M, Citterio F, Wiecek A, Scheuermann EH, Klinger M, Russ G, Pescovitz MD, Prestele H. Polyomavirus BK replication in de novo kidney transplant patients receiving tacrolimus or cyclosporine: a prospective, randomized, multicenter study. Am J Transplant. 2013;13(1):136–45. https://doi.org/10.1111/j.1600-6143.2012.04320.x.

8. Brennan DC, Agha I, Bohl DL, Schnitzler MA, Hardinger KL, Lockwood M, Torrence S, Schuessler R, Roby T, Gaudreault-Keener M, Storch GA. Incidence of BK with tacrolimus versus cyclosporine and impact of preemptive immunosuppression reduction. Am J Transplant. 2005;5(3):582–94.

9. Schmitt C, Raggub L, Linnenweber-Held S, Adams O, Schwarz A, Heim A. Donor origin of BKV replication after kidney transplantation. J Clin Virol. 2014;59(2):120–5. https://doi.org/10.1016/j.jcv.2013.11.009.

10. Schwarz C, Lawitschka A, Bohmig GA, Dauber EM, Greinix H, Kozakowski N, Muhlbacher F, Berlakovich GA, Wekerle T. Kidney transplantation with corticosteroids alone after haploidentical HSCT from the same donor. Transplantation. 2016;100(10):2219–21. https://doi.org/10.1097/TP.0000000000001213.

11. Visweh V, Yost SE, Kaplan B. The prevalence and implications of BK virus replication in non-renal solid organ transplant recipients: a systematic review. Transplant Rev (Orlando). 2015;29(3):175–80. https://doi.org/10.1016/j.trre.2015.02.004.

12. Sawinski D, Trofe-Clark J. BKV viremia and development of de novo DSA in renal transplant recipients. Clin Transpl. 2015;31:249–56.

13. Papadimitriou JC, Randhawa P, Rinaldo CH, Drachenberg CB, Alexiev B, Hirsch HH. BK polyomavirus infection and renourinary tumorigenesis. Am J Transplant. 2016;16(2):398–406. https://doi.org/10.1111/ajt.13550.

14. Hirsch HH, Randhawa P, Practice ASTIDCo. BK polyomavirus in solid organ transplantation. Am J Transplant. 2013;13(Suppl 4):179–88. https://doi.org/10.1111/ajt.12110.

15. Kidney Disease: Improving Global Outcomes Transplant Work G. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant. 2009;9(Suppl 3):S1–155. https://doi.org/10.1111/j.1600-6143.2009.02834.x.

16. Nickeleit V, Singh HK, Randhawa P, Drachenberg CB, Bhatnagar R, Bracamonte E, Chang A, Chon WJ, Dadhania D, Davis VG, Hopfer H, Mihatsch MJ, Papadimitriou JC, Schaub S, Stokes MB, Tungekar MF, Seshan SV, Banff Working Group on Polyomavirus N. The Banff Working Group classification of definitive polyomavirus nephropathy: morphologic definitions and clinical correlations. J Am Soc Nephrol. 2018;29(2):680–93. https://doi.org/10.1681/ASN.2017050477.

17. Johnston O, Jaswal D, Gill JS, Doucette S, Fergusson DA, Knoll GA. Treatment of polyomavirus infection in kidney transplant recipients: a systematic review. Transplantation. 2010;89(9):1057–70. https://doi.org/10.1097/TP.0b013e3181d0e15e.

18. Dharnidharka VR, Cherikh WS, Abbott KC. An OPTN analysis of national registry data on treatment of BK virus allograft nephropathy in the United States. Transplantation. 2009;87(7):1019–26. https://doi.org/10.1097/TP.0b013e31819cc383.

19. van Doesum WB, Gard L, Bemelman FJ, de Fijter JW, Homan van der Heide JJ, Niesters HG, van Son WJ, Stegeman CA, Groen H, Riezebos-Brilman A, Sanders JSF. Incidence and outcome

of BK polyomavirus infection in a multicenter randomized controlled trial with renal transplant patients receiving cyclosporine-, mycophenolate sodium-, or everolimus-based low-dose immunosuppressive therapy. Transpl Infect Dis. 2017;19(3). https://doi.org/10.1111/tid.12687

20. Comoli P, Hirsch HH, Ginevri F. Cellular immune responses to BK virus. Curr Opin Organ Transplant. 2008;13(6):569–74. https://doi.org/10.1097/MOT.0b013e3283186b93.

21. 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(12):2727–35. https://doi.org/10.1111/j.1600-6143.2007.01984.x.

22. Schaenman JM, Korin Y, Sidwell T, Kandarian F, Harre N, Gjertson D, Lum EL, Reddy U, Huang E, Pham PT, Bunnapradist S, Danovitch GM, Veale J, Gritsch HA, Reed EF. Increased frequency of BK virus-specific polyfunctional CD8+ T cells predict successful control of BK viremia after kidney transplantation. Transplantation. 2017;101(6):1479–87. https://doi.org/10.1097/TP.0000000000001314.

23. Cioni M, Leboeuf C, Comoli P, Ginevri F, Hirsch HH. Characterization of immunodominant BK polyomavirus 9mer epitope T cell responses. Am J Transplant. 2016;16(4):1193–206. https://doi.org/10.1111/ajt.13598.

24. Barrett AJ, Prockop S, Bollard CM. Virus specific T cells: broadening applicability. Biol Blood Marrow Transplant. 2017. https://doi.org/10.1016/j.bbmt.2017.10.004

25. Davies SI, Muranski P. T cell therapies for human polyomavirus diseases. Cytotherapy. 2017. https://doi.org/10.1016/j.jcyt.2017.08.011

26. Pastrana DV, Ray U, Magaldi TG, Schowalter RM, Cuburu N, Buck CB. BK polyomavirus genotypes represent distinct serotypes with distinct entry tropism. J Virol. 2013;87(18):10105–13. https://doi.org/10.1128/JVI.01189-13.

27. Randhawa P, Pastrana DV, Zeng G, Huang Y, Shapiro R, Sood P, Puttarajappa C, Berger M, Hariharan S, Buck CB. Commercially available immunoglobulins contain virus neutralizing antibodies against all major genotypes of polyomavirus BK. Am J Transplant. 2015;15(4):1014–20. https://doi.org/10.1111/ajt.13083.

28. Vu D, Shah T, Ansari J, Naraghi R, Min D. Efficacy of intravenous immunoglobulin in the treatment of persistent BK viremia and BK virus nephropathy in renal transplant recipients. Transplant Proc. 2015;47(2):394–8. https://doi.org/10.1016/j.transproceed.2015.01.012.

29. Josephson MA, Gillen D, Javaid B, Kadambi P, Meehan S, Foster P, Harland R, Thistlethwaite RJ, Garfinkel M, Atwood W, Jordan J, Sadhu M, Millis MJ, Williams J. Treatment of renal allograft polyoma BK virus infection with leflunomide. Transplantation. 2006;81(5):704–10. https://doi.org/10.1097/01.tp.0000181149.76113.50.

30. Faguer S, Hirsch HH, Kamar N, Guilbeau-Frugier C, Ribes D, Guitard J, Esposito L, Cointault O, Modesto A, Lavit M, Mengelle C, Rostaing L. Leflunomide treatment for polyomavirus BK-associated nephropathy after kidney transplantation. Transpl Int. 2007;20(11):962–9. https://doi.org/10.1111/j.1432-2277.2007.00523.x.

31. Elfadawy N, Flechner SM, Liu X, Schold J, Tian D, Srinivas TR, Poggio E, Fatica R, Avery R, Mossad SB. The impact of surveillance and rapid reduction in immunosuppression to control BK virus-related graft injury in kidney transplantation. Transpl Int. 2013;26(8):822–32. https://doi.org/10.1111/tri.12134.

32. Williams JW, Javaid B, Kadambi PV, Gillen D, Harland R, Thistlewaite JR, Garfinkel M, Foster P, Atwood W, Millis JM, Meehan SM, Josephson MA. Leflunomide for polyomavirus type BK nephropathy. N Engl J Med. 2005;352(11):1157–8. https://doi.org/10.1056/NEJM200503173521125.

33. Rinaldo CH, Hirsch HH. Antivirals for the treatment of polyomavirus BK replication. Expert Rev Anti-Infect Ther. 2007;5(1):105–15. https://doi.org/10.1586/14787210.5.1.105.

34. Knoll GA, Humar A, Fergusson D, Johnston O, House AA, Kim SJ, Ramsay T, Chasse M, Pang X, Zaltzman J, Cockfield S, Cantarovich M, Karpinski M, Lebel L, Gill JS. Levofloxacin for BK virus prophylaxis following kidney transplantation: a randomized clinical trial. JAMA. 2014;312(20):2106–14. https://doi.org/10.1001/jama.2014.14721.

35. Lee BT, Gabardi S, Grafals M, Hofmann RM, Akalin E, Aljanabi A, Mandelbrot DA, Adey DB, Heher E, Fan PY, Conte S, Dyer-Ward C, Chandraker A. Efficacy of levofloxacin in the treatment of BK viremia: a multicenter, double-blinded, randomized, placebo-controlled trial. Clin J Am Soc Nephrol. 2014;9(3):583–9. https://doi.org/10.2215/CJN.04230413.
36. Wu SW, Chang HR, Lian JD. The effect of low-dose cidofovir on the long-term outcome of polyomavirus-associated nephropathy in renal transplant recipients. Nephrol Dial Transplant. 2009;24(3):1034–8. https://doi.org/10.1093/ndt/gfn675.
37. Tylden GD, Hirsch HH, Rinaldo CH. Brincidofovir (CMX001) inhibits BK polyomavirus replication in primary human urothelial cells. Antimicrob Agents Chemother. 2015;59(6):3306–16. https://doi.org/10.1128/AAC.00238-15.
38. Reisman L, Habib S, McClure GB, Latiolais LS, Vanchiere JA. Treatment of BK virus-associated nephropathy with CMX001 after kidney transplantation in a young child. Pediatr Transplant. 2014;18(7):E227–31. https://doi.org/10.1111/petr.12340.
39. Wollebo HS, White MK, Gordon J, Berger JR, Khalili K. Persistence and pathogenesis of the neurotropic polyomavirus JC. Ann Neurol. 2015;77(4):560–70. https://doi.org/10.1002/ana.24371.
40. Querido S, Jorge C, Sousa H, Birne R, Matias P, Weigert A, Adragao T, Bruges M, Ramos S, Santos M, Paixao P, Curran MD, Machado D. JC polyomavirus nephropathy confirmed by using an in-house polymerase chain reaction method. Transpl Infect Dis. 2015;17(5):732–6. https://doi.org/10.1111/tid.12426.
41. Bialasiewicz S, Hart G, Oliver K, Agnihotri SP, Koralnik IJ, Viscidi R, Nissen MD, Sloots TP, Burke MT, Isbel NM, Burke J. A difficult decision: atypical JC polyomavirus encephalopathy in a kidney transplant recipient. Transplantation. 2017;101(6):1461–7. https://doi.org/10.1097/TP.0000000000001275.
42. Yang D, Keys B, Conti DJ, Foulke L, Stellrecht K, Cook L, Lopez-Soler RI. JC polyomavirus nephropathy, a rare cause of transplant dysfunction: case report and review of literature. Transpl Infect Dis. 2017;19(2). https://doi.org/10.1111/tid.12654
43. Moreno-Estebanez A, Almeida Velasco J, Perez-Concha T, Gonzalez-Pinto T, Gabilondo I. Progressive multifocal leukoencephalopathy 11 years after liver transplantation: a case report. J Neurovirol. 2017. https://doi.org/10.1007/s13365-017-0578-0
44. Mateen FJ, Muralidharan R, Carone M, van de Beek D, Harrison DM, Aksamit AJ, Gould MS, Clifford DB, Nath A. Progressive multifocal leukoencephalopathy in transplant recipients. Ann Neurol. 2011;70(2):305–22. https://doi.org/10.1002/ana.22408.
45. Plavina T, Subramanyam M, Bloomgren G, Richman S, Pace A, Lee S, Schlain B, Campagnolo D, Belachew S, Ticho B. Anti-JC virus antibody levels in serum or plasma further define risk of natalizumab-associated progressive multifocal leukoencephalopathy. Ann Neurol. 2014;76(6):802–12. https://doi.org/10.1002/ana.24286.
46. Berger JR, Aksamit AJ, Clifford DB, Davis L, Koralnik IJ, Sejvar JJ, Bartt R, Major EO, Nath A. PML diagnostic criteria: consensus statement from the AAN neuroinfectious disease section. Neurology. 2013;80(15):1430–8. https://doi.org/10.1212/WNL.0b013e31828c2fa1.
47. Pavlovic D, Patera AC, Nyberg F, Gerber M, Liu M, Progressive Multifocal Leukoencephalopathy C. Progressive multifocal leukoencephalopathy: current treatment options and future perspectives. Ther Adv Neurol Disord. 2015;8(6):255–73. https://doi.org/10.1177/1756285615602832.
48. Vulliemoz S, Lurati-Ruiz F, Borruat FX, Delavelle J, Koralnik IJ, Kuntzer T, Bogousslavsky J, Picard F, Landis T, Du Pasquier RA. Favourable outcome of progressive multifocal leucoencephalopathy in two patients with dermatomyositis. J Neurol Neurosurg Psychiatry. 2006;77(9):1079–82. https://doi.org/10.1136/jnnp.2006.092353.
49. Balduzzi A, Lucchini G, Hirsch HH, Basso S, Cioni M, Rovelli A, Zincone A, Grimaldi M, Corti P, Bonanomi S, Biondi A, Locatelli F, Biagi E, Comoli P. Polyomavirus JC-targeted T-cell therapy for progressive multiple leukoencephalopathy in a hematopoietic cell transplantation recipient. Bone Marrow Transplant. 2011;46(7):987–92. https://doi.org/10.1038/bmt.2010.221.

50. Marzocchetti A, Tompkins T, Clifford DB, Gandhi RT, Kesari S, Berger JR, Simpson DM, Prosperi M, De Luca A, Koralnik IJ. Determinants of survival in progressive multifocal leukoencephalopathy. Neurology. 2009;73(19):1551–8. https://doi.org/10.1212/WNL.0b013e3181c0d4a1.
51. Ho J, Jedrych JJ, Feng H, Natalie AA, Grandinetti L, Mirvish E, Crespo MM, Yadav D, Fasanella KE, Proksell S, Kuan SF, Pastrana DV, Buck CB, Shuda Y, Moore PS, Chang Y. Human polyomavirus 7-associated pruritic rash and viremia in transplant recipients. J Infect Dis. 2015;211(10):1560–5. https://doi.org/10.1093/infdis/jiu524.
52. Siebrasse EA, Nguyen NL, Smith C, Simmonds P, Wang D. Immunohistochemical detection of KI polyomavirus in lung and spleen. Virology. 2014;468–470:178–84. https://doi.org/10.1016/j.virol.2014.08.005.
53. Bialasiewicz S, Rockett RJ, Barraclough KA, Leary D, Dudley KJ, Isbel NM, Sloots TP. Detection of recently discovered human polyomaviruses in a longitudinal kidney transplant cohort. Am J Transplant. 2016;16(9):2734–40. https://doi.org/10.1111/ajt.13799.