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REVIEW

BK Virus Nephropathy: Prevalence, Impact and Management Strategies

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Abstract: BK virus reactivation as a result of therapeutic immunosuppression following renal transplant can result in BK polyomavirus nephropathy and renal allograft loss. This is a complex and challenging clinical problem with a range of management options and practices reported in literature. The current standard for early diagnosis and treatment is surveillance by measuring viral DNA in blood using qPCR. Immunosuppression reduction is the cornerstone of effective management but is associated with a risk of acute rejection following treatment.

Keywords: BK polyomavirus nephropathy, kidney transplant, immune monitoring, treatment, surveillance

Prevalence

BK polyoma virus (BKV) is a non-enveloped DNA virus first discovered in the urine of a kidney transplant recipient in 1971.[1] Its genome has an early region which codes for the large and small T antigens, a late region which codes for the capsid proteins VP1-3, and agnoprotein, and a non-coding control region (NCCR). BKV strains have six genotypes based on polymorphisms in VP1 and NCCR.[2]

BKV is widely prevalent in general population with over 80% individuals having antibodies against BK virus.[3,4] The most common mode of transmission is through respiratory secretions, resulting in a mild self-limited respiratory infection.[5] Viral spread to other organs is believed to be via bloodstream and in immunocompetent individuals, it remains clinically silent in renal tubular epithelium.

"Presumptive" BK Polyoma virus nephropathy (PVN) is defined as persistently high BK viral load in plasma >10,000 copies/mL for four weeks. Renal allograft biopsy remains the gold standard for diagnosing "definite" PVN.[6–12] Since the allograft involvement is focal, and the possibility of sampling error is high, two cores containing medulla are required for an adequate biopsy sample.[8,9] Intragraft polyomavirus gene expression on renal biopsy has recently been reported as a useful adjunct to the diagnosis of PVN with the potential to differentiate from T-cell-mediated rejection.[13] Biopsy proven "definite" PVN has an incidence of 5–6%, with a higher incidence in ABO-incompatible donors and following desensitization in highly sensitized recipients.[14–16]

The Banff Working Group on Polyomavirus Nephropathy recently published a morphologic classification of definite PVN into three groups, Class I, II, and III, based on polyomavirus load and Banff ci score (interstitial fibrosis) for ease of diagnostic communication and comparative data analysis.[17] However, this was

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a retrospective observational analysis which has not been validated in a mixed population.

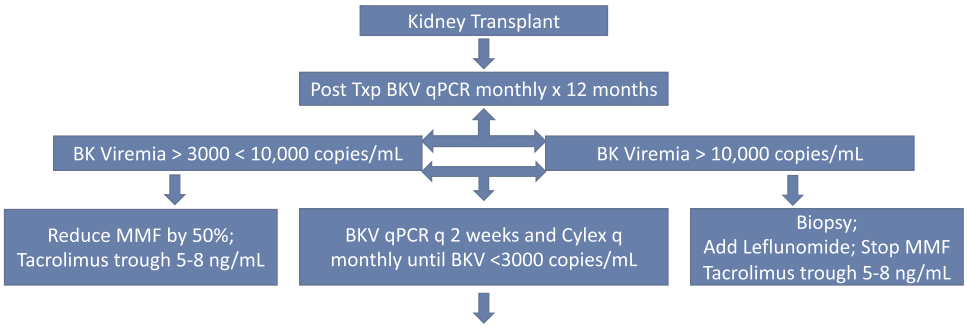
Impact

BK-virus-related disease is commonly seen in kidney transplant and hematopoietic stem cell transplant recipients. The cause for reactivation is therapeutic immunosuppression (IS) following transplant.[18] BK viruria can be seen in 60% of kidney transplant recipients, while BK viremia is seen in up to 13% kidney transplant recipients, and nephropathy in 10%.[19–21] The actual reported incidence varies; however, with the choice of induction IS, maintenance IS, and screening modality used, hence the wide variations in literature. In US, 5.7%– 7.5% of renal allografts are lost to PVN.[22]

PVN is therefore a serious clinical problem in kidney transplantation. PVN is difficult to treat since there is no BKV-specific anti-viral therapy. Any anti-virals currently in use work poorly and suffer from substantial host toxicity. PVN is treated by stimulating host immune response by IS reduction; however, there is a risk of acute rejection following virus clearance,[23] further complicating treatment options since rejection treatment requires escalation of IS which often results in BKV recurrence.

The current standard for management is monitoring for viral DNA using qPCR. Other investigational surveillance tools include monitoring BKV-specific CMIR,[24] and donor-derived cell-free DNA (dd-cfDNA). dd-cfDNA is a non-specific marker of injury. Since BKV causes interstitial inflammation and tubulitis, elevated levels of dd-cfDNA have been reported in a study of allograft rejection in kidney transplant in the setting of PVN.[25] Since BKV is also known to be associated with development of de novo donor-specific antibodies (DSA),[26] elevated dd-cfDNA levels in this infection could actually represent alloantibody-mediated microcirculation injury. Persistent viremia (lasting >140 days) was found to be strongly associated with development of Class II DSAs. The association of Class II DSA with antibody-mediated rejection (ABMR) and graft loss is well known.[27]

Most studies have found that humoral immune response does not play a significant role in preventing development of PVN.[28] Despite the presence of a high level of antibodies, patients with PVN can have high levels of viral load and low CD8+ T cells.[29] BKV-specific cell-mediated immune response (CMIR) was demonstrated in normal individuals to be the mechanism responsible for prevention of BKV reactivation in immunocompetent individuals.[30] Low levels of BKV-specific interferon-gamma (IFNγ) producing T cells correlate with progression to PVN, while reconstitution of these cells correlates with resolution of nephropathy.[31–34] Immune monitoring could help in identifying patients at risk of PVN;[34–38] however, this knowledge is still evolving and has not been used in guiding treatment recommendations.



Cylex	BKV qPCR (copies/mL)		
	< 3,000	3000 – 10,000	> 10,000
< 225	Resume Baseline IS	Reduce MMF by 50%; Tacrolimus trough 5-8 ng/mL	Add Leflunomide; Stop MMF Tacrolimus trough 5-8 ng/mL
225 - 500	Resume Baseline IS	Reduce MMF by 50%; Tacrolimus trough 8-10 ng/mL	Leflunomide; Reduce MMF by 50%; Tacrolimus trough 5-8 ng/mL; Cidofovir if refractory
> 500	Resume Baseline IS	Leflunomide; Reduce MMF by 50%; Tacrolimus trough 8-10 ng/mL; Cidofovir if refractory	Leflunomide; Reduce MMF by 50%; Tacrolimus trough 8-10 ng/mL; Cidofovir if refractory

Figure 1 Monitoring and treatment protocol for BK viremia at our center.

Management Strategies

Risk Factors

The most common factor associated with risk of developing PVN is the intensity of immunosuppression. Donor factors associated with a higher risk include transplanting kidney from BKV seropositive donor to seronegative donor,[39,40] number of HLA mismatches, ABO-incompatibility, and ischemia reperfusion injury.[6,14,41,42] Recipient factors include old age, male sex, desensitization, and prior kidney transplant with PVN.[16,43]

Surveillance

The mainstay of treatment of PVN is immunosuppression reduction. A wide variation in treatment practices is observed based on individual clinician experience. Most centers monitor BKV post-transplant at 3, 6, 9, and 12 months.[44] However, with more intense induction regimen or in those with risk factors, it is prudent to perform routine surveillance at monthly intervals in the first 12 months following transplant. This is standard in our center. In addition to following viral loads with qPCR, we also follow ImmuKnow Immune Cell Function Assay (Cylex Inc., Columbia, MD, USA) as an indirect measure of CMIR. Our approach is outlined in Figure 1.

Immunosuppression Reduction and Antiviral Therapy

For BKV viral load <10,000 copies/mL, IS dose reduction should be considered. For viral loads >10,000 copies/mL, a common initial approach involves calcineurin inhibitor dose reduction by 25–50%. Switching to Cyclosporine A (CsA) has been shown to have some benefit as well.[45] Switching from Tacrolimus to CsA is a common approach used in our center in patients with persistent viremia; However, a higher incidence of biopsy-proven acute rejection is seen with this approach.[46] Failure of reduction in viral load should prompt reduction of mycophenolate mofetil (MMF) by 50%, or discontinuation of MMF or switching to an mTOR inhibitor.[47,48] Switching from MMF to Leflunomide is another option associated with favorable outcomes.[49–52] We routinely switch from MMF to Leflunomide in our center; however, the practices vary by center and physician experience. In refractory cases, most common therapeutic option is Cidofovir, use of which is limited by its nephrotoxicity.[53–55] Brincidofovir is a prodrug of cidofovir and has also been used with limited success.[56,57] IVIG preparations have high titers of neutralizing antibodies to BK virus and can help expedite virus clearance and have been used as a useful adjunctive therapy.[58–61] Fluoroquinolones have been tried but failed to show

Table 1 Anti-Virals for PVN

Anti-Virals			
Name	**Class/Mechanism**	**Dose**	**Comments**
Leflunomide[49–52]	Anti-Inflammatory; Anti-Viral; Immunosuppressive	PO: Loading- 100 mg daily for 3–5 days; maintenance- 20-60 mg qD; Trough Level −50-100 μg/mL	Can be used following discontinuation of MMF.
Cidofovir[53–55]	Nucleoside analog	IV: 0.25–1.0 mg/Kg at 1–3 weeks	Used in refractory cases; Nephrotoxicity is the most serious adverse effect.
Brincidofovir[56,57]	Investigational Prodrug of Cidofovir; Anti-viral activity	PO: 2 mg/Kg twice weekly	Reasonably well tolerated; Investigational.
Intravenous immunoglobulin (IVIG)[58–61]	Immunoglobulin preparation with high titers of neutralizing antibodies to BK virus	IV: 0.25–2.0 g/Kg	Can be used as an adjunct to other measures in refractory cases.
Levofloxacin[62–64]	Fluoroquinolones; Antiviral, inhibit helicase activity of large T antigen	PO: 500 mg qD (renally adjusted)	Levofloxacin failed to show benefit in randomized controlled trials.
Everolimus[47,48]	Inhibits mammalian target of rapamycin (mTOR) kinase activity, inhibiting T and B lymphocyte activation and proliferation.	PO 0.75 mg twice daily adjusted to trough levels of 3–8 ng/mL.	Can be used following discontinuation of MMF. Limited literature supporting its use.

therapeutic benefit.[62–64] There is no strong evidence supporting antiviral treatment for PVN;[46] however, for patients with persistent BK viremia despite adequate immunosuppression reduction, therapeutic options are outlined in Table 1.

Conclusion

Due to lack of strong evidence, no strong treatment recommendations can be made; however, it is prudent to start with immunosuppression reduction and add anti-virals for persistent viremia not responding to immunosuppression reduction based on physician experience. Regular monitoring of qPCR remains the cornerstone of early diagnosis and treatment. Novel monitoring strategies being investigated include immune monitoring and ddcf DNA.

Abbreviations

BKV, BK virus; NCCR, non-coding control region; PVN, BK polyoma virus nephropathy; qPCR, quantitative polymerase chain reaction; ddcfDNA, donor-derived cell-free DNA; DSA, donor-specific antibodies; ABMR, antibody-mediated rejection; CMIR, cell-mediated immune response; JCV, JC virus; IFNγ, interferon-gamma; MMF, mycophenolate mofetil; CsA, cyclosporine A; ATP, adenosine triphosphate; ELISPOT, enzyme-linked immunoSpot; IS, Immunosuppression; PML, progressive multifocal leukoencephalopathy.

Disclosure

The authors report no conflicts of interest in this work.

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