Monitoring of BK virus infection in pediatric kidney transplant recipients

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Polyomavirus BK (BKV) is one of important causes of allograft dysfunction and graft loss in kidney transplant recipients. The clinical manifestation of BKV infection includes BK viuria, BK viremia, and BKV nephropathy (BKVN) and is commonly developed during the first post-transplantation year. Additionally, BK viremia is very common in children with kidney transplant, especially in younger children and in those receiving a kidney from cadaveric donors. BKV infection can be diagnosed via detection of decoy cells in urine cytology, confirming the presence of Haufen, which are icosahedral aggregates of polyomavirus particles, by electron microscope, and detection of BKV DNA in urine and blood polymerase chain reaction (PCR). Among them, measurement of BKV DNA load in blood by PCR is regarded as more preferred method to diagnose BKV infection due to high sensitivity and specificity as well as cost-effectiveness than other methods such as urine PCR and decoy cell. Diagnosis of BKVN is made by allograft biopsy that shows tubulointerstitial mononuclear infiltration with many plasma cells, degenerative change in tubules and intranuclear polyomavirus inclusion via SV40 immunoperoxidase stain.

In many studies, it was reported that routine monitoring of BKV reactivation and adequate reduction of immunosuppression alone can resolve viremia, preserve allograft function and prevent symptomatic BKVN effectively. Kwon et al. also reported that BKV infection was developed in nine of thirty three pediatric kidney transplant recipients (27.3%) and effectively resolved by reduction of calcineurin inhibitor via routine monitoring of BKV load. Until now, although there are several anti-BKV agents such as leflunomide, cidofovir, intravenous immunoglobulin and fluoroquinolone, benefit of these agents is limited. Therefore, preemptive approach to resolution of BKV viuria and/or viremia before development of BKVN with reduction of immunosuppression is the mainstay of therapy in BK viremia/BKVN. The 2009 Kidney Disease: Improving Global Outcomes (KDIGO) clinical
practice guidelines recommend reduction in immunosuppression when BKV plasma NAT (nucleic acid testing) results are persistently greater than $10^4$ copies/mL.

According to clinical algorithm based on current guideline and available evidences (Fig.1), screening for BK virus reactivation is recommended at least monthly for the first 3-6 months after kidney transplantation, then every 3 months until the end of the first year posttransplant. In addition, this is also recommended at unexplained rise in serum creatinine or after treatment of acute rejection. If a patient present elevated serum creatinine and significant viremia (BK viral load > $10^4$ copies/mL on PCR), graft biopsy should be performed to confirm definitive BKVN.

There is one thing to consider here. Allograft dysfunction combined with significant BK viremia doesn’t always mean BKVN only. Because it is difficult to exclude the possibility of acute rejection or BKVN combined with acute rejection in this situation, abrupt reduction of immunosuppression without confirming the pathologic finding of definitive BKVN can be counter-productive. Unfortunately, Kwon et al. reported that six of nine patients with significant BK viremia presented azotemia, but renal biopsy was not performed in them, so this is one of a few limitations in their study. In conclusion, routine screening of BK virus reactivation and active application of graft biopsy are most reliable ways to overcome BK virus infection in pediatric kidney transplant recipients.

**Conflict of interest**

No potential conflict of interest relevant to this article was reported.
References


Fig. 1. Clinical algorithm of management of BK virus infection in kidney transplant recipients

* Blood PCR(+): significant viremia (BK viral load > 10⁴ copies/mL)

** Other therapies: IVIG, cidofovir, leflunomide, and fluoroquinolone, etc.

BKV, BK virus; PCR, polymerase chain reaction; IVIG, intravenous immunoglobulin.
BKV DNA load by PCR (urine & blood)

1) Monthly x 6, then month 9, 12, then annually up to 5 years post-transplantation
2) Unexplained rise in serum creatinine
3) After treatment of acute rejection

Urine PCR(+)/blood PCR(-)

- Monthly blood PCR for the first year, then every 3 months
  - If blood PCR(+)

Urine PCR(+)/blood PCR(+)*

- Allograft dysfunction(-)
  - Reduction in immunosuppression and repeat test in 2-4 weeks until clear

- Allograft dysfunction(+)
  - Allograft biopsy
    - Acute rejection
    - BKV nephropathy
    - Acute rejection + BKV nephropathy

If blood PCR(+)

- Treat acute rejection

BKV nephropathy

1) Reduction in immunosuppression
2) Consider IVIG, cidofovir, leflunomide, fluoroquinolone

Treat acute rejection with subsequent decrease in maintenance immunosuppression & other therapies**