

BK Virus Screening and Management Following Kidney Transplantation: An Update

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Abstract

BK virus is a ubiquitous human virus with a peak incidence of primary infection in children 2-5 years of age and a seroprevalence rate of greater than 60-90% among the adult population worldwide. Following primary infection, BK virus preferentially establishes latency within the genitourinary tract and frequently reactivates in the setting of immunosuppression. In renal transplant recipients, BK virus is associated with a range of clinical syndromes including asymptomatic viremia with or without viremia, ureteral stenosis and obstruction, interstitial nephritis, and BK allograft nephropathy (BKN). BKN most commonly presents with an asymptomatic rise in serum creatinine between 2 to 60 months after engraftment (median 9 months). A definitive diagnosis requires an allograft biopsy. Over the last two decades, BKN has been recognized as an important cause of allograft dysfunction and graft loss in kidney transplant recipients. Nonetheless, there is currently no standardized protocol for the management of BK viremia or established BKN. In this article, a brief overview of the literature on the various treatment strategies for BK-associated clinical spectrum is presented followed by the authors' suggested approach for posttransplant screening and monitoring for BK virus replication. Suggested treatment strategies are also discussed.

Keywords: BKV screening and management; Kidney transplantation; BKV viremia; BKV viremia; BK nephropathy; Antiviral therapy in BK associated clinical syndromes; Intravenous immunoglobulin (IVIG)

Literature Overview

Although treatment strategies for BK viremia with or without BK nephropathy vary widely among centers, immunological containment of BK virus replication has been accepted as the mainstay of therapy. Suggested strategies for reduction in immunosuppression include reduction or discontinuation of antimetabolites (mycophenolate mofetil or azathioprine), reduction in calcineurin inhibitor therapy, or immunosuppressant class switch.

Registry analyses and prospective randomized clinical trials suggested that tacrolimus is associated with a higher risk of BK reactivation than cyclosporine (CSA) [1-3]. In an analysis of the Organ Procurement Transplantation Network (OPTN) database consisting of more than 48,000 primary kidney transplant recipients, the cumulative incidence of treatment of BK infection within the first 2 years posttransplant was shown to be significantly higher in patients treated with tacrolimus than those receiving CSA maintenance immunosuppression at discharge (4.0% vs. 1.7%, respectively, $p < 0.001$) [1]. The same study also demonstrated a lower incidence of BK treatment in patients who did not receive antimetabolite at discharge compared with those who received mycophenolate mofetil (MMF) at discharge. Similar to registry data, results of the DIRECT study (in which *de novo* transplant recipients were randomized to receive either CSA or tacrolimus) revealed a lower incidence of BK viremia in CSA-treated patients compared with their tacrolimus-treated counterparts at 1-year (4.8% vs. 12.1%, $p = 0.004$) [3]. *In vitro* studies suggest that CSA may exert an antiviral effect on BKV *via* suppression of viral replication [4,5] whereas tacrolimus has been reported to activate BKV replication in primary human tubular epithelial cells *via* the FK-binding protein 12 pathway [6]. Nonetheless, not all studies demonstrated a lower incidence of BK viremia with tacrolimus compared with CSA-treated patients [7]. Single-center studies suggest that tacrolimus and MMF combination therapy result in a significantly higher incidence of BK viremia/BKN compared with other regimens. It is hypothesized that tacrolimus-MMF create a permissive immunosuppressive environment for BKV replication [8].

Early anecdotal case reports demonstrated that tacrolimus to cyclosporine or sirolimus conversion therapy resulted in resolution of BKN and viremia/viuria. Recent experimental animal models have shown that mTOR inhibition may promote differentiation of antiviral memory CD8 T-lymphocytes [9] and enhance their magnitude and quality [10]. Analysis of the OPTN registry database demonstrated a lower 2-year cumulative incidence of "treatment for BK" (as reported on the kidney follow-up forms) in primary kidney transplant recipients receiving mTOR inhibitor therapy at hospital discharge ($n = 5380$) when compared with patients on other regimens without mTOR inhibitor ($n = 42,912$, 1.74% vs. 3.67%, respectively, $p < 0.001$) [1].

In BKV-associated disease refractory to reduction in immunosuppressive therapy alone, antiviral agents such as cidofovir, leflunomide, intravenous immunoglobulins (IVIG) [11] and fluoroquinolones have been used in anecdotal case reports and small series of patients with variable success. Nonetheless, systemic review of 40 studies (3 randomized controlled trials, 2 prospective cohort, 6 retrospective cohort, and 29 case series studies) showed no graft survival benefit of adding cidofovir or leflunomide to immunosuppressive reduction for the management of BKN [12]. Experimental studies suggest that human intravenous immune globulin (IVIG) preparations contain BKV neutralizing antibodies [13]. However, the role of these antibodies in clearing viral infection remains to be explored. In a single-center study consisting of 70 renal transplant recipients with BKV infection, Bohl et al. [14] showed that while there was a strong

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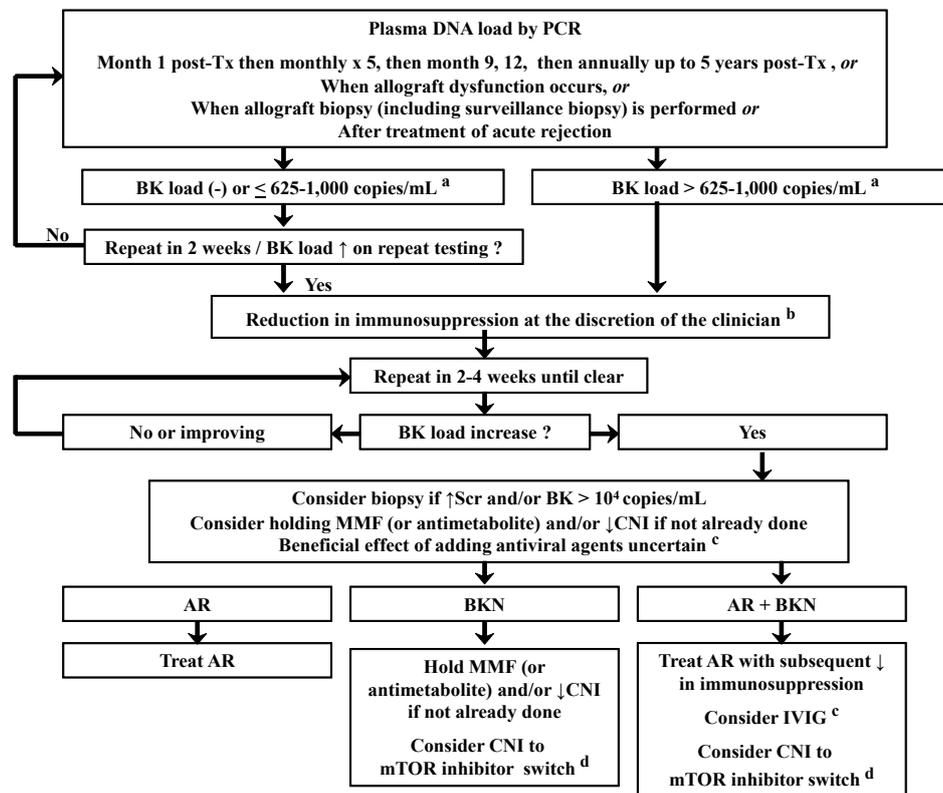
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relationship between the intensity of BKV infection and IgG BKV-specific antibody titers, no association between antibody response and viral clearance was observed. It is speculated that humoral response offers incomplete protection and adequate control of BK involves virus-specific cellular immune response. The detection of interferon- γ secretion from BK virus-specific T cells has been shown to be associated with resolution of BK viremia [15]. Fluoroquinolones have been shown to inhibit BK DNA topoisomerase and SV40 large tumor antigen (T antigen) helicase. Limited data suggest that fluoroquinolones are effective at preventing BK viremia after renal transplantation [16]. The cidofovir lipid conjugate CMX001 (currently under development for CMV prophylaxis) has been shown in *in vitro* studies to have anti-polyomavirus activity. Its use in recipients of hematopoietic cell transplant has shown promise for mitigation of BK virus-associated complications [17]. Whether CMX001 might prove to be effective in the treatment of BKV-associated clinical syndromes awaits studies.

Early reports showed a 30% to greater than 60% progressive decline in renal function and graft loss in patients with established BKN despite various treatment strategies. More recent studies demonstrated that early diagnosis and intervention may improve prognosis. In a retrospective 5-year review of an open-label, prospective trial of renal transplant recipients randomized to receive either tacrolimus or CSA, minimization of immunosuppression upon detection of viremia was found to be associated with excellent 5-year graft survival (84%), low rejection rates (12%), and excellent allograft function (eGFR 63 mL/min for tacrolimus- and 52 mL/min for cyclosporine-treated patients) [7]. In the study, antimetabolite was withdrawn upon detection of BK viremia, and calcineurin inhibitor minimized in cases of sustained viremia. There was no difference in overall graft loss between patients with and without viremia or sustained viremia. Furthermore, there was no evidence of clinical BKN at 5 year follow-up.



^a No standardized PCR assays for BKV are currently available. Cut-off levels for viral detection should be based on PCR assays used at individual institutions

^b **Common practice:** 1) \downarrow or Hold MMF (or antimetabolite) 2) \downarrow (MMF + CNI) by 25-50% 3) \downarrow CNI. **Less common practice:** 1) \downarrow Prednisone +/- \downarrow CNI 2) Tacrolimus to CSA switch 3) CNI to mTOR inhibitor switch +/- \downarrow MMF (ongoing clinical trials)

^c See text

^d Evidence-based recommendations are lacking. May avoid long-term nephrotoxic effect of CNI therapy. Not recommended in patients with baseline significant proteinuria (arbitrarily defined as ≥ 500 mg/24hr)

Abbreviations: Post-Tx: post-transplant; SCR: serum creatinine; MMF: mycophenolate mofetil; CNI: calcineurin inhibitor; AR: acute rejection; BKN: BK nephropathy; mTOR: mammalian target of rapamycin; IVIG: intravenous immunoglobulins

Figure 1: Suggested approach for screening & management of BKV-associated clinical syndromes.

Treatment Strategies for BK-Associated Clinical Syndromes: The KDOQI Guidelines and the Authors' Perspective

The KDOQI guidelines

The 2009 KDIGO clinical practice guidelines suggested screening all renal transplant recipients for BKV with quantitative plasma NAT (nucleic acid testing) at least monthly for the first 3-6 months after transplantation, then every 3 months until the end of the first post transplant year, whenever there is an unexplained rise in serum creatinine, and after treatment for acute rejection [18]. The guidelines suggest reducing immunosuppressive medications when BKV plasma NAT is persistently greater than 10,000 copies/mL.

The authors' perspective

Owing to the lack of evidence-based treatment options targeting viral replication and high rates of graft loss in established BKN, intensive monitoring of urine and/or serum for BK by polymerase chain reaction (PCR) and judicious reduction of immunosuppressive therapy is warranted. A proactive, preemptive approach often leads to resolution of viuria and/or viremia and halts the progression of BK viremia to BK nephropathy. Studies have demonstrated that the highest prevalence of BK viuria and viremia occurs at 2-3 months, and 3-6 months, respectively. Hence, it seems plausible to monitor for BK viuria and/or viremia at least monthly for the first 3-6 months after transplantation. Steroid pulses used to treat rejection without reduction in maintenance immunosuppression have been shown to be associated with an increased incidence of BK viuria, viremia and nephropathy [19]. Analyses of US transplant registry database also demonstrated an increase in the incidence of "treatment for BK (polyoma) virus" (as reported on the kidney follow-up forms) in patients receiving induction therapy with rabbit antithymocyte globulin (Thymoglobulin) compared with those receiving IL-2 receptor antagonist induction [1,20]. Hence, it would be reasonable to screen patients for BKV after treatment for acute rejection particularly when T-lymphocyte depleting agent is used.

While the KDOQI guidelines recommend reduction in immunosuppression when BKV plasma NAT is persistently greater than 10^4 copies/mL, in the authors' opinion rising plasma BKV DNA copies on serial measurements also warrants immunosuppression reduction irrespective of BKV copy levels. Although monitoring for urine or plasma BK or both is largely institution dependent, monitoring for plasma BK alone appears to be cost effective because BKN is unusual in the absence of BK viremia. Patients with biopsy-proven BKN and concurrent acute rejection should be treated with antirejection treatment, with subsequent reduction in immunosuppression at the discretion of the clinicians. Anecdotal case reports suggested that IVIG may be effective in treating steroid-resistant rejection and its use may be beneficial in patients with concomitant rejection and BKN or in those with histopathological changes that are indistinguishable from those of rejection [21,22].

Although tacrolimus and MMF combination therapy has been shown to result in a significantly higher incidence of BK viuria/BKN compared with cyclosporine-MMF therapy, further studies are needed before tacrolimus to CSA switch for BK viremia/BKN can be routinely recommended. It is noteworthy that mycophenolic acid concentrations are lower in patients receiving CSA-based immunosuppression compared to those treated with tacrolimus containing regimen. It is speculated that tacrolimus-MMF combination therapy can lead

to higher overall degree of immunosuppression and increased BK replication risk. While MMF dosing was significantly lower in patients randomized to tacrolimus compared to CSA in the DIRECT study, pharmacokinetic studies to assess mycophenolic acid drug exposure were not performed. Whether calcineurin inhibitor to mTOR inhibitor class switch is beneficial in patients with BK viremia or BKN or both is a subject of ongoing clinical research. The effectiveness of currently available antiviral agents are of uncertain benefit. Lastly, the routine recommendations of fluoroquinolone prophylactic therapy in the post transplant period awaits results of randomized, double-blind, placebo-controlled trials.

The authors' suggested approach for post transplant screening and management of BKV-associated clinical syndromes are shown in figure 1. BKV-specific immune response and development of T-cell and antibody-based vaccines against BKV are subjects of future research.

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