Open Access

OBM Transplantation

LIDSEN Publishing Inc.

Review

BK Virus Infection and Its Management in Renal Transplantation: An Update

Uttayan Chakrabarti [1], Manish Chaurvedy [1], Nitin Kumar Bajpai [1], Jitendra Goswami [2], Rajesh Kumar Garsa [3], Rajesh Jhorawat [1,*]

1. All India Institute of Medical Sciences (AIIMS) Jodhpur, India; E-Mails: uttayanchakrabarti@gmail.com; drmanishchaturvedy@gmail.com; drnitinbajpai@gmail.com; jhorawat2000@gmail.com
2. Manipal Hospitals, Jaipur, India; E-Mail: goswamidoc@gmail.com
3. Fortis Escorts Hospital, Jaipur, India; E-Mail: rajeshgarsa@gmail.com

* **Correspondence:** Rajesh Jhorawat; E-Mail: jhorawat2000@gmail.com

Academic Editor: Deborah B. Adey

Special Issue: Complications and Management of Kidney Transplantation: Focus on Infection

OBM Transplantation
2023, volume 7, issue 3
doi:10.21926/obm.transplant.2303192

Received: April 10, 2023
Accepted: July 06, 2023
Published: July 14, 2023

Abstract

BK virus (BKV) is a common opportunistic pathogen in kidney transplant recipients and one of the most challenging causes of allograft dysfunction and loss. Although over-immunosuppression remains the primary risk factor for BKV infection after transplantation, male gender, older recipient age, prior rejection episodes, degree of human leukocyte antigen mismatching, prolonged cold ischemia time, BK virus serostatus and ureteral stent placement have all been implicated as risk factors. Routine screening post-renal transplant is important to prevent allograft loss in patients with BK viruria or viremia. Reduction of immunosuppression remains the mainstay of BKV nephropathy treatment and is the most studied intervention. In this review, we are going to discuss the epidemiology of BK virus infection, screening strategies, treatment options and new studies or evidence in the future.

Keywords
BK virus nephropathy; renal transplantation; immunosuppression; viruria; viremia

1. Introduction

BK virus (BKV) is a common opportunistic pathogen in kidney transplant recipients and one of the most challenging causes of allograft dysfunction and loss. This virus was named after a Sudanese kidney transplant recipient with ureteric stenosis who was the first patient to have BKV isolated from urine [1]. BK virus is a small DNA virus that establishes lifelong infection in the renal tubular and uroepithelial cells of most of the world's population. Though quiescent and benign in the majority, immunocompromised BKV can reactivate, and in some, lead to BKV-associated nephropathy (BKVAN). BKV reactivation is common among kidney transplant recipients and is a risk factor for premature allograft loss. Therefore screening for reactivation is recommended for all kidney transplant recipients after transplantation. Reduction of immunosuppression is the cornerstone of management, and no specific antiviral or immunomodulatory therapy is sufficiently effective for routine use.

2. Epidemiology

2.1 Prevalence

BKV is a ubiquitous virus with a worldwide seroprevalence of 80-90 percent. Primary infection is usually acquired in childhood, possibly via fecal-oral or respiratory transmission. The virus establishes lifelong infection in renal tubular and uroepithelial cells following primary infection. For most individuals, primary and persistent infections are clinically silent and not associated with known adverse effects [2].

Among kidney transplant recipients, reactivation of latent infection or transmission of new infection via the donor's kidney can lead to viruria (detection of intact virus or virus components in urine), viremia (detection of viral DNA in thae blood), or allograft nephropathy (demonstration of virus or virus components in allograft tissue) [3]. Viral replication commonly occurs during the first year after transplant when cellular immunity is most suppressed. Viruria and viremia are detected in approximately 25-30 and 12 percent of kidney transplant recipients, respectively [4], and almost invariably precede the development of nephropathy in a stereotypical pattern of viruria, followed by viremia, followed by BKV-associated nephropathy (BKVAN). Approximately 1-10 percent of kidney transplant recipients will develop BKVAN [5]. Though historically associated with more than 50% [6] graft loss rates, with the implementation of standardized screening protocols, rates of short-term graft loss have fallen substantially [4].

2.2 Risk Factors

The intensity of immunosuppression appears to be a dominant risk factor for BKV replication and disease. Replication rates are higher in the early posttransplant period and following treatment for allograft rejection when the intensity of immunosuppression is highest. Thymoglobulin, either as

induction therapy or treatment of rejection, increases the risk for BKV infection whereas neither alemtuzumab nor interleukin 2 receptor antibody (i.e., basiliximab) use appears to increase the risk [7]. The risk for BKV replication is increased with higher cumulative steroid dose [8], corticosteroid pulses as rejection treatment, and steroid maintenance compared with steroid withdrawal regimens [7].

No specific immunosuppressive drug or regimen has been definitively associated with clinically significant BKV infection [9]. Several studies have suggested that certain drugs (particularly tacrolimus) may be associated with an increased relative risk [7]. In contrast, others (e.g., mammalian [mechanistic] target of rapamycin [mTOR] inhibitors) may be associated with a lower relative risk [10]. However, BKV replication and BKVAN have occurred in patients receiving nearly all immunosuppressive drugs and their combinations [9]. High-risk serostatus (i.e., kidney transplant from a BKV-seropositive donor to a seronegative recipient) [11], impaired immune response to BKV [11], and donor BKV viruria prior to transplant [12] contribute to higher risk. Other risk factors with an increased risk of BKVAN include older age [13], ureteral stent placement [14], ABO incompatibility [15], rejection or ischemia of the transplanted kidney [16], delayed graft function [14], HLA mismatch [15], specific HLA-C alleles [17], BKV polymorphisms [18], and transplantation from an HCV-positive donor [19]. Factors associated with decreased risk include recipient HLA-B51 positivity [20], and polycystic kidney disease [21].

2.3 Virology

BK polyomavirus is a small (30 to 45 nm), icosahedral, nonenveloped, double-stranded, closed circular DNA virus [22]. The 5 kb genome encodes six viral proteins-two "early" nonstructural or enzymatic proteins, an apoprotein, and three "late" proteins. The early proteins are the large tumor antigen or "T antigen," the small tumor antigen, or the "t antigen." The T antigen is responsible for cell immortalization and the establishment of latent infection. The agnoprotein helps in the assembly of viral particles. The three "late" viral capsid proteins, VP-1, VP-2, and VP-3, mediate cell entry and progeny virion assembly.

Mutations in noncoding control regions can be progressively acquired during an infection, leading to altered cell tropism, permissivity (i.e., cell types supporting viral replication), and replication rates [18]. Virulence may also vary among serotypes, which differ genetically and in their cellular tropism. Serotype I is the most prevalent and is responsible for most human diseases. Neutralizing antibodies to one serotype does not appear to confer protection against others [23].

2.4 Pathogenesis

Insufficient cellular immune control is presumed to be an important part of BKVAN pathogenesis [24]. After primary infection, which typically occurs in childhood, BKV maintains persistent infection in the renal and uroepithelium (transitional epithelium, renal tubular epithelium, and parietal epithelium of Bowman's capsule) of most individuals [25]. Control of this persistent infection is dependent on CD4+ and CD8+ T cell immunity [26]. When immune control is disrupted as with immunosuppressive drugs, BKV begins to actively replicate.

As viral replication persists, injury to the renal tubular epithelium results from direct viral replication and cell turnover. Subsequent inflammation and fibrosis lead to further injury and ultimately tubular atrophy, necrosis, and nephron loss [27]. The inflammatory milieu may further

promote viral replication and perpetuate injury [8]. Transcriptional analysis of kidney allograft tissue in BKVAN has demonstrated the upregulation of multiple inflammatory pathways that overlap considerably with those seen in acute allograft rejection [28].

2.5 Clinical Manifestations

ssBKV replication typically develops in stages in kidney transplant recipients: viruria followed by viremia if viral replication persists, nephropathy.

2.6 Viruria and Viremia

Viruria is the earliest manifestation of BKV infection in kidney transplant recipients, affecting approximately one-quarter to one-third of patients during the first year of transplantation [4]. Viruria is mostly asymptomatic, detected only by screening, and does not progress to viremia. Though viruria is a sensitive marker for progression to BKVAN, it is nonspecific [29]. Shedding of BKV in the urine as detected by PCR methods is common among otherwise healthy older adult patients, pregnant women, and patients with suppressed cellular immunity. It is generally without any clinical consequence [30]. Urine decoy cells (renal tubular or uroepithelial cells containing intranuclear viral inclusions), which typically represent higher-level viruria, may be present at this stage. However, they do not have a significant prognostic value for progression to viremia than detection of viruria by more sensitive methods such as PCR.

Viremia may follow viruria in a few weeks and occurs most frequently in those with high urine viral loads and sustained viruria. Viremia is detected in 10 to 30 percent of recipients in the first six months posttransplantation and 5 to 10 percent thereafter. Viremia is typically asymptomatic. However, viremia carries a greater predictive value than viruria for progression to BKVAN [31]. Viremia is present in nearly all patients with BKVAN and has a positive predictive value of approximately 40 to 65 percent for the development of BKVAN. Since BKVAN can follow viremia (usually within one to two weeks) and the graft damage can be irreversible, viremia is generally accepted as an indication to reduce immunosuppression. Higher viral loads and sustained viremia have greater predictive value for concomitant or progression to biopsy-confirmed BKVAN [32].

2.7 BKV-Associated Nephropathy (BKVAN)

Asymptomatic viruria, viremia, and/or a slow progressive rise in serum creatinine are typically the only indicators of BKVAN. The incidence of BKVAN is highest in the first 6 months posttransplant. While most cases occur in the first posttransplant year, they can occur years after transplant. The incidence of late BKVAN appears to be highest in patients with multi-organ transplants and is possibly related to the more intensive immunosuppressive regimens [33].

Progressive kidney allograft dysfunction and graft loss can ensue over months without resolution of infection [27]. Early infection triggers interstitial inflammation within the allograft progressing to fibrosis and tubular injury. Urinalysis may reveal pyuria, hematuria, cellular casts of renal tubular cells and inflammatory cells, or may be normal. Reduction of immunosuppression is the primary means of restoring immunity and control of BKV replication. However, this also carries a risk of rejection, which can be difficult to distinguish clinically from progressive BKVAN [34].

2.8 Ureteral Stenosis

BKV infection has been implicated in late ureteral stenosis (>1 month posttransplantation). Ureteral infection is initially focal, followed by a destructive phase in which the uroepithelium and smooth muscle cells are affected. This phase is characterized by marked inflammation and ulcerations, ultimately leading to ureteral stenosis. Clinically it is characterized by asymptomatic hydronephrosis leading to a decline in GFR with the diagnosis confirmed by ultrasound. BKV replication should therefore be sought for in cases of late ureteral stenosis especially in mid ureteric strictures [35].

2.9 Other Manifestations

Case reports exist of BKV causing pneumonitis, retinitis, vasculopathy, meningoencephalitis, and Guillain-Barre syndrome, among other manifestations [36]. Hemorrhagic cystitis is a rare manifestation of BKV infection in kidney transplant recipients and is mostly reported in hematopoietic cell transplant recipients [37]. There is a putative link between BKV and the development of genitourinary cancers, largely based on animal models [38]. However, a causal role for BKV and human malignancies has not been established.

2.10 Screening and Diagnosis

Patients should be screened with a quantitative plasma BKV PCR at the following time points:

- Monthly for the first six months following transplant, then every three months until two years posttransplant, and then annually until five years posttransplant [39].
- Whenever kidney allograft dysfunction occurs or when an allograft biopsy is performed for allograft dysfunction [40].

Generally, levels >1000 copies/mL are considered positive in most assays, and levels >10,000 copies/mL correlate with biopsy-confirmed BKVAN. For patients with viremia (e.g., viral loads >1000 copies/mL) and normal allograft function, the immunosuppression is reduced and viral load is monitored every 2-4 weeks to ensure it is downtrending. For patients with viremia and new-onset allograft dysfunction, the immunosuppression is reduced and viral loads are monitored every 2-4 weeks after that when the clinical picture points towards BKVAN. Allograft biopsy should be considered if the cause for allograft dysfunction is uncertain or if kidney dysfunction and/or viremia fail to resolve despite reducing immunosuppression [41].

3. Testing Methods

3.1 Plasma Quantitative PCR

Quantification of plasma BKV DNA by real-time polymerase chain reaction (PCR) is the preferred screening test for BKVAN [39]. It is both sensitive (100%) and specific (88%) for the diagnosis of BKVAN and has a higher positive predictive value for BKVAN than the detection of viruria by urine quantitative PCR or urine cytology (50 to 60 percent versus 40 and 29 percent, respectively) [5].

Plasma PCR can monitor the patient's response to therapy since a decrease in BKV viremia usually occurs soon after a reduction in immunosuppression and precedes a decrease in viruria by weeks to months [9]. Even in the absence of histologic evidence of BKVAN, persistent high-grade viremia

is associated with worse allograft function and risk of allograft loss [27]. Though no established threshold levels for BKV viremia predict BKVAN most centers agree that a BKviral load of ≥10,000 copies/mL, particularly when sustained for more than three weeks duration is highly suggestive of BKVAN [39].

3.2 Urine Quantitative PCR

Urine quantitative PCR for BKV DNA is not recommended though some centers prefer it given its high sensitivity and less invasive nature. Patients found to have viruria require confirmation with quantitative plasma PCR as around half of the patients with BK viruria will not develop viremia or BKVAN [42]. Furthermore, urine PCR for BKV DNA is not as useful as plasma PCR for monitoring the response to therapy as changes in the urine viral load lag behind the plasma viral load upon lowering immunosuppression. However, some studies suggest that the detection of high-grade viruria might be helpful to predict clinically significant viremia [31].

3.3 Urine Cytology

Although the presence of characteristic cytopathologic changes in infected cells (which have been called decoy cells due to their resemblance to renal carcinoma cells) is strongly suggestive of BKV infection, urine cytology is less sensitive and specific for the diagnosis of BKVAN compared with plasma quantitative PCR. The diagnostic utility is further limited by interobserver variability and this test's qualitative, rather than quantitative, nature [5].

3.4 Donor-Derived Cell-Free DNA (dd-cfDNA)

The association of dd-cfDNA with plasma BK viral loads and biopsy findings was evaluated in a study to determine whether dd-cfDNA can distinguish asymptomatic BKV from BKVAN [43]. It demonstrated that higher dd-cfDNA levels were associated with higher BK viral loads, biopsy-diagnosed BVAN, and histologic changes meeting Banff criteria for T-cell-mediated rejection. These preliminary findings show that dd-cfDNA may be a useful noninvasive test to assess for progression of BKV to BKVAN [44].

3.5 Kidney Allograft Biopsy

Kidney allograft biopsy is the gold standard for diagnosing BKVAN, assessing its severity, and evaluating concomitant processes. However, since biopsy is invasive and associated with sampling, a presumptive diagnosis is often made based on significant viremia (plasma BK viral load ≥10,000 copies/mL).

A definitive diagnosis of BKVAN requires the following findings on kidney biopsy [45]:

- Characteristic cytopathic changes plus.
- Positive immunohistochemistry tests using antibodies directed specifically against BKV or against the cross-reacting SV40 large T antigen. Positive SV40 staining is associated with a specificity of almost 100% for polyomavirus nephropathy, although it does not distinguish between BKV and JC virus-associated cases.

Because of the focal nature of early BKVAN, the diagnosis may be missed in one-third of biopsies. As a result, at least two biopsy cores, preferably including the medulla, should be examined as BKV

is more likely to be present in the medulla. A repeat biopsy should be considered if the initial biopsy does not confirm BKVAN [45].

3.6 Histologic Findings

BKVAN is associated with characteristic histologic findings on kidney biopsy:

- Intranuclear basophilic viral inclusions without a surrounding halo.
- Anisonucleosis, hyperchromasia, and chromatin clumping of infected cells.
- Interstitial mononuclear or polymorphonuclear cell infiltrates the areas of tubular damage.
- Tubular injury, is characterized by tubular cell apoptosis, cell dropout, desquamation, and flattened epithelial lining.
- Tubulitis, which is manifested by lymphocyte permeation of the tubular basement membrane. When extensive, it is difficult to differentiate BKVAN from allograft rejection [25].

With electron microscopy, intranuclear viral inclusions (with a diameter size of 30 to 50 nm) and tubular damage characterized by tubular cell necrosis, lysosomal inclusions, and luminal protein and cellular casts are seen.

The Banff Working Group on Polyomavirus Nephropathy 2017 established a classification system that defined three histologic classes of definitive (biopsy-proven) BKVAN based on two morphologic variables: intrarenal polyomavirus replication/load levels (pvl) and Banff interstitial fibrosis (ci) score [46]. The pvl score is based on the extent of virally induced tubular changes. A tubule with intranuclear viral inclusion bodies (type 1 or 2) and/or a positive immunohistochemical reaction for SV40 large T antigen in one or more cells per tubular cross-section is considered "a positive tubule." The overall percentage of positive tubular cross-sections is estimated in the entire biopsy sample (i.e., all available cores and all tubules/ducts in the cortex and medulla) and three levels of pvl are defined: pvl 1 ≤ 1 percent, pvl 2 = 1 to 10 percent, pvl 3 ≥ 10 percent positive tubules/ducts. The three histologic classes of PVN are as follows [46]:

- PVN class 1 – pvl 1, ci ≤ 1
- PVN class 2 – pvl 1, ci ≥ 2 or pvl 2, any ci score or pvl 3, ci ≤ 1
- PVN class 3 – pvl 3, ci ≥ 2

Though found to correlate with clinical outcomes [46] in a retrospective analysis of 178 patients, the same correlation was not documented across all studies [47]. SV40 T antigen stain may be falsely negative due to sampling error and/or limited staining sensitivity. Persistent high-level viremia is the most significant risk factor for allograft loss. However, no single clinical or pathologic feature could predict the clinical course of BKVAN in an individual patient. A high proportion of cases eventually evolve into interstitial fibrosis and tubular atrophy despite the treatment of BKVAN which highlights the importance of prevention over treatment strategies [41].

3.7 Distinguishing BKVAN from Rejection

Allograft rejection may closely resemble BKVAN on kidney biopsy [28]. Distinguishing BKVAN from allograft rejection is important since treatment for presumed rejection with increased immunosuppression may result in allograft loss if BKVAN is present. BKVAN is distinguished by the presence of BKV inclusions and immunohistologic or in situ hybridization evidence of virally infected cells, usually tubular epithelial cells, rather than podocytes or endothelial cells [48]. It is important to correlate the histologic findings with PCR evidence of viremia.

Diagnosing concomitant T cell-mediated rejection and BKVAN is difficult because of similar histologic features [28]. Extensive tubulitis in areas remote from the viral cytopathic changes suggests that acute rejection BKVAN are present. The combined presence of endarteritis, fibrinoid vascular necrosis, glomerulitis, and C4d deposits along peritubular capillaries is conclusive evidence of concurrent rejection. However, some patients with BKVAN without concurrent rejection may have C4d deposits in the tubular basement membrane [49]. In some patients, distinguishing BKV infection from rejection may be possible by empirically altering the immunosuppressive regimen and observing the clinical response.

3.8 Other Diagnostic Methods

Negative-staining electron microscopy of the urine of patients with BKVAN often reveals cast-like, three-dimensional polyomavirus aggregates, termed Haufen. Haufen form in injured tubules with BKV replication and a high intratubular uromodulin concentration and are excreted like other urinary casts. In one cohort study of >300 kidney transplant recipients, the detection of Haufen in voided urine had a sensitivity, specificity, negative predictive value, and positive predictive value for biopsy-proven BKVAN of greater than 95 percent [50], suggesting that this might be a noninvasive way to diagnose BKVAN. However the limiting factor lies in the usage of electron microscopy for diagnosis. Therefore it is not a widely used screening test, however may be used in certain scenarios, such as in pediatric patients or when a kidney allograft biopsy cannot be safely performed.

3.9 Treatment

With no specific antiviral therapies, the cornerstone of BKVAN management is reduced immunosuppression. This approach applies to both the prevention of BKVAN in detected BKV viremia and the treatment of established BKVAN. Protocols, however, vary among centers and are often individualized.

3.10 Reduction of Immunosuppression

Approaches to reducing immunosuppression vary among centers, and no randomized controlled trials directly compare different protocols. A plasma BKV quantitative PCR is obtained prior to the reduction of immunosuppression. It is monitored every 1-2 weeks until BKV DNA is undetectable for two consecutive tests obtained at least one week apart. The serum creatinine level is monitored weekly. If it increases by ≥25 percent from baseline at any time during reduction of immunosuppression, evaluation should be done for a possible acute rejection.

For patients not having concurrent acute rejection and on triple immunosuppression (calcineurin inhibitor, antimetabolite, steroid), the antimetabolite is reduced by 50 percent. The antimetabolite is completely discontinued if the BKV viral load does not decrease within 2-4 weeks. If there is still no decrease in viral load after another two weeks, the CNI dosage is reduced by 25-50 percent, targeting a whole blood tacrolimus trough level of 4 to 6 ng/mL or a whole blood cyclosporine trough level of 60 to 100 ng/mL. An alternative approach is to first decrease the CNI dosage by 25 to 50 percent, then reduce the antimetabolite by 50 percent, and discontinue the antimetabolite [39].

A similar approach can be followed for patients on steroid-free regimens as for patients on triple immunosuppression. Alternatively, both the CNI and antimetabolite dosage can be reduced

concomitantly, allowing targeting of two pathways and lowering the total immunosuppression. In one meta-analysis of observational data from 40 studies, graft loss rates were similar when comparing the reduction in immunosuppression alone versus the reduction of immunosuppression plus either cidofovir or leflunomide [51]. Similar findings have been reported in subsequent cohort studies [52].

3.11 Role of Adjunctive Therapies

The initial approach of decreasing immunosuppressives is effective in most patients. For those with progressive allograft dysfunction despite a maximal decrease in immunosuppressive therapy for a period of several weeks to months and who also have severe hypogammaglobulinemia (IgG <400 mg/dl), IVIg can be attempted though the efficacy is unproven. Suppose administered is usually given at a dose of 300 mg/kg every 3 weeks along with a reduction of immunosuppression with a repeat IgG trough level after 3 months of therapy with a goal of IgG >400 mg/dl [53-56].

There is no role of leflunomide, cidofovir, or quinolone antibiotics [49].

Leflunomide is a prodrug with its active metabolite having both immunosuppressive and antiviral activity [57]. However, the routine use of leflunomide is avoided in view of its uncertain efficacy, long half-life, potential for hematologic toxicity and hepatotoxicity, wide interpatient variability in metabolism, and the inability to easily monitor the active metabolite level. Studies on the efficacy of leflunomide have yielded mixed results. Though an initial case series showed an improvement of BKVAN with a reduction of tacrolimus trough level to 4-6 ng/ml and prednisolone 5-10 mg with mycophenolate mofetil being replaced by leflunomide, these results were not reciprocated in other studies [57-59]. In the phase II randomized trial, an investigational agent derived from an active metabolite of leflunomide (FK778) also provided no clinically significant benefit compared with the reduction of immunosuppressive agents [60].

Though initially thought to have anti-BKV activity, RCTs have shown no benefit of quinolones as prophylactic therapy following transplantation or as treatment of active BK viremia [61, 62].

Cidofovir, a nucleotide analog of cytosine has demonstrated modest in vitro activity against polyomaviruses with its use demonstrated in a few uncontrolled studies [63, 64]. However, given its potential nephrotoxicity the use should only be restricted to cases where other interventions have failed.

3.12 Experimental Therapies

Based upon the important role of cellular and humoral immune mechanisms in control of BKV infection and the absence of other proven treatments, immune-based therapies in the form of Virus-specific T cells (ClinicalTrials.gov identifier: NCT04605484) and BKV-specific monoclonal antibodies (ClinicalTrials.gov identifier: NCT04294472) are being actively assessed for safety, tolerability, and antiviral effect in human clinical trials [41].

3.13 Prognosis

Following BKVAN, many patients experience allograft dysfunction and loss [46], with a 3-year allograft survival of 79% compared to 90% in patients without BKVAN [65]. BKVAN has also been associated with developing class II de novo donor-specific antibodies, a risk factor for allograft

failure [66]. It remains unclear whether immunosuppression can be safely increased after the resolution of BKV infection. An individualized approach is advised considering the immunological risk of the patient and close monitoring of GFR, BK viremia, and donor-specific antibodies.

3.14 Concurrent BKVAN and Acute Rejection

There are no data to guide the optimal management. Some would advocate treating the acute rejection first (e.g., with pulse glucocorticoids) followed by a reduction of immunosuppression once the patient has a clinical response to antirejection treatment (i.e., a decrease in serum creatinine level) [39]. However, more frequent monitoring of BK viremia may be warranted if immunosuppression is augmented. Others would avoid augmented immunosuppression and favor a reduction in maintenance immunosuppression alone [9].

3.15 Acute Rejection after Reduction of Immunosuppression

Acute rejection can occur in 8-12% of kidney transplant recipients with BK viremia or established BKVAN following a reduction in immunosuppression [67]. Acute rejection should be suspected when serum creatinine increases after the decrement of immunosuppression. An allograft biopsy is helpful in such settings to establish the same. The optimal management of such patients varies among centers. Generally augmentation of immunosuppression is avoided if patients have biopsy-proven BKVAN and are maintained at the same reduced level when the patient developed rejection.

3.16 Kidney Retransplantation

Retransplantation in patients with graft failure due to BKVAN is a reasonable option and has been successfully performed [68]. BKV replication's absence should be confirmed before retransplantation [49], although successful pre-emptive, living, related kidney transplants have been reported during active BKVAN with viremia [69]. Close screening is mandated following retransplantation with BKVAN. Some centers would recommend avoiding intense immunosuppression. There is no high-quality data for nephrectomy of the failed allograft or of the native kidneys, which may serve as a reservoir and a source of reinfection. Available data suggest that retransplantation is associated with good graft outcomes in those who have lost their first allograft due to BKVAN [70].

4. Conclusion

BK virus is a common opportunistic pathogen in kidney transplant recipients which can lead to allograft dysfunction and loss. Over-immunosuppression is the primary risk factor for BKV infection after transplantation. Routine screening post-renal transplant is important for early detection and immediate action to prevent graft loss. Reduction of immunosuppression remains the mainstay of BKV nephropathy treatment at present.

Author Contributions

Dr Uttayan- Preparation, editing and Review of literature; Dr Rajesh Jhorawat- Review of literature, editing and Preparation of manuscript; Rest author help in Review of literature and editing of the manuscript.

Competing Interests

The authors have declared that no competing interests exist.

References

1. Moens U, Calvignac-Spencer S, Lauber C, Ramqvist T, Feltkamp MC, Daugherty MD, et al. ICTV virus taxonomy profile: Polyomaviridae. J Gen Virol. 2017; 98: 1159-1160.
2. Knowles WA, Pipkin P, Andrews N, Vyse A, Minor P, Brown DW, et al. Population-based study of antibody to the human polyomaviruses BKV and JCV and the simian polyomavirus SV40. J Med Virol. 2003; 71: 115-123.
3. Gupta M, Miller F, Nord EP, Wadhwa NK. Delayed renal allograft dysfunction and cystitis associated with human polyomavirus (BK) infection in a renal transplant recipient: A case report and review of literature. Clin Nephrol. 2003; 60: 405-414.
4. Sánchez DM, Garcia LJ, Jiménez IL, Luján IS, Soriano MG, Viñas SL, et al. Renal function impairment in kidney transplantation: Importance of early BK virus detection. Transplant Proc. 2019; 51: 350-352.
5. Hirsch HH, Knowles W, Dickenmann M, Passweg J, Klimkait T, Mihatsch MJ, et al. Prospective study of polyomavirus type BK replication and nephropathy in renal-transplant recipients. N Engl J Med. 2002; 347: 488-496.
6. Vasudev B, Hariharan S, Hussain SA, Zhu YR, Bresnahan BA, Cohen EP. BK virus nephritis: Risk factors, timing, and outcome in renal transplant recipients. Kidney Int. 2005; 68: 1834-1839.
7. 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: 1019-1026.
8. Hirsch HH, Vincenti F, Friman S, Tuncer M, Citterio F, Wiecek A, et al. Polyomavirus BK replication in de novo kidney transplant patients receiving tacrolimus or cyclosporine: A prospective, randomized, multicenter study. Am J Transplant. 2013; 13: 136-145.
9. Brennan DC, Agha I, Bohl DL, Schnitzler MA, Hardinger KL, Lockwood M, et al. Incidence of BK with tacrolimus versus cyclosporine and impact of preemptive immunosuppression reduction. Am J Transplant. 2005; 5: 582-594.
10. Moscarelli L, Caroti L, Antognoli G, Zanazzi M, Di Maria L, Carta P, et al. Everolimus leads to a lower risk of BKV viremia than mycophenolic acid in de novo renal transplantation patients: A single-center experience. Clin Transplant. 2013; 27: 546-554.
11. Abend JR, Changala M, Sathe A, Casey F, Kistler A, Chandran S, et al. Correlation of BK virus neutralizing serostatus with the incidence of BK viremia in kidney transplant recipients. Transplantation. 2017; 101: 1495-1505.

12. Schwarz A, Linnenweber-Held S, Heim A, Framke T, Haller H, Schmitt C. Viral origin, clinical course, and renal outcomes in patients with BK virus infection after living-donor renal transplantation. Transplantation. 2016; 100: 844-853.
13. Demey B, Tinez C, Francois C, Helle F, Choukroun G, Duverlie G, et al. Risk factors for BK virus viremia and nephropathy after kidney transplantation: A systematic review. J Clin Virol. 2018; 109: 6-12.
14. Chong S, Antoni M, Macdonald A, Reeves M, Harber M, Magee CN. BK virus: Current understanding of pathogenicity and clinical disease in transplantation. Rev Med Virol. 2019; 29: e2044.
15. Sharif A, Alachkar N, Bagnasco S, Geetha D, Gupta G, Womer K, et al. Incidence and outcomes of BK virus allograft nephropathy among ABO-and HLA-incompatible kidney transplant recipients. Clin J Am Soc Nephrol. 2012; 7: 1320-1327.
16. Bohl DL, Brennan DC. BK virus nephropathy and kidney transplantation. Clin J Am Soc Nephrol. 2007; 2: S36-S46.
17. Bohl DL, Storch GA, Ryschkewitsch C, Gaudreault-Keener M, Mark AS, Major EO, et al. Donor origin of BK virus in renal transplantation and role of HLA C7 in susceptibility to sustained BK viremia. Am J Transplant. 2005; 5: 2213-2221.
18. Funk GA, Steiger J, Hirsch HH. Rapid dynamics of polyomavirus type BK in renal transplant recipients. J Infect Dis. 2006; 193: 80-87.
19. Molnar MZ, Potluri VS, Schaubel DE, Sise ME, Concepcion BP, Forbes RC, et al. Association of donor hepatitis C virus infection status and risk of BK polyomavirus viremia after kidney transplantation. Am J Transplant. 2022; 22: 599-609.
20. Wunderink HF, Haasnoot GW, de Brouwer CS, van Zwet EW, Kroes AC, de Fijter JW, et al. Reduced risk of BK polyomavirus infection in HLA-B51–positive kidney transplant recipients. Transplantation. 2019; 103: 604-612.
21. Plafkin C, Singh T, Astor BC, Parajuli S, Bhutani G, Safdar N, et al. Kidney transplant recipients with polycystic kidney disease have a lower risk of post-transplant BK infection than those with end-stage renal disease due to other causes. Transpl Infect Dis. 2018; 20: e12974.
22. Helle F, Brochot E, Handala L, Martin E, Castelain S, Francois C, et al. Biology of the BKPyV: An update. Viruses. 2017; 9: 327.
23. Pastrana DV, Ray U, Magaldi TG, Schowalter RM, Çuburu N, Buck CB. BK polyomavirus genotypes represent distinct serotypes with distinct entry tropism. J Virol. 2013; 87: 10105-10113.
24. Schachtner T, Stein M, Babel N, Reinke P. The loss of BKV-specific immunity from pretransplantation to posttransplantation identifies kidney transplant recipients at increased risk of BKV replication. Am J Transplant. 2015; 15: 2159-2169.
25. Drachenberg CB, Beskow CO, Cangro CB, Bourquin PM, Simsir A, Fink J, et al. Human polyoma virus in renal allograft biopsies: Morphological findings and correlation with urine cytology. Hum Pathol. 1999; 30: 970-977.
26. Ambalathingal GR, Francis RS, Smyth MJ, Smith C, Khanna R. BK polyomavirus: Clinical aspects, immune regulation, and emerging therapies. Clin Microbiol Rev. 2017; 30: 503-528.
27. Nankivell BJ, Renthawa J, Sharma RN, Kable K, O'Connell PJ, Chapman JR. BK virus nephropathy: Histological evolution by sequential pathology. Am J Transplant. 2017; 17: 2065-2077.

28. Mannon RB, Hoffmann SC, Kampen RL, Cheng OC, Kleiner DE, Ryschkewitsch C, et al. Molecular evaluation of BK polyomavirus nephropathy. Am J Transplant. 2005; 5: 2883-2893.
29. Elfadawy N, Yamada M, Sarabu N. Management of BK polyomavirus infection in kidney and kidney-pancreas transplant recipients: A review article. Infect Dis Clin. 2018; 32: 599-613.
30. McClure GB, Gardner JS, Williams JT, Copeland CM, Sylvester SK, Garcea RL, et al. Dynamics of pregnancy-associated polyomavirus urinary excretion: A prospective longitudinal study. J Med Virol. 2012; 84: 1312-1322.
31. Madden K, Janitell C, Sower D, Yang S. Prediction of BK viremia by urine viral load in renal transplant patients: An analysis of BK viral load results in paired urine and plasma samples. Transpl Infect Dis. 2018; 20: e12952.
32. Pinto GG, Poloni JA, Rotta LN, Razonable RR, Pasqualotto AC. Screening for BK virus nephropathy in kidney transplant recipients: Comparison of diagnostic tests. Braz J Nephrol. 2016; 38: 356-362.
33. Imlay H, Whitaker K, Fisher CE, Limaye AP. Clinical characteristics and outcomes of late-onset BK virus nephropathy in kidney and kidney-pancreas transplant recipients. Transpl Infect Dis. 2018; 20: e12928.
34. Baek CH, Kim H, Yu H, Yang WS, Han DJ, Park SK. Risk factors of acute rejection in patients with BK nephropathy after reduction of immunosuppression. Ann Transplant. 2018; 23: 704-712.
35. Mylonakis E, Goes N, Rubin RH, Cosimi AB, Colvin RB, Fishman JA. BK virus in solid organ transplant recipients: An emerging syndrome. Transplantation. 2001; 72: 1587-1592.
36. Reploeg MD, Storch GA, Clifford DB. BK virus: A clinical review. Clin Infect Dis. 2001; 33: 191-202.
37. Kerbauy LN, Kerbauy MN, Bautzer V, Chapchap EC, de Mattos VR, da Rocha JD, et al. Severe hemorrhagic cystitis caused by the BK polyomavirus is associated with decreased survival post-allogeneic hematopoietic stem cell transplantation. Transpl Infect Dis. 2019; 21: e13101.
38. Abend JR, Jiang M, Imperiale MJ. BK virus and human cancer: Innocent until proven guilty. Semin Cancer Biol. 2009; 19: 252-260.
39. Hirsch HH, Randhawa PS, AST Infectious Diseases Community of Practice. BK polyomavirus in solid organ transplantation-Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019; 33: e13528.
40. KDIGO Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant. 2009; 9: S1-S155.
41. Limaye AP, Brennan D, Blumberg EA, Bond S. Kidney transplantation in adults: BK polyomavirus-associated nephropathy. Waltham, MA, USA: UpToDate; 2020.
42. Laskin BL, Goebel J. Cost-efficient screening for BK virus in pediatric kidney transplantation: A single-center experience and review of the literature. Pediatr Transplant. 2010; 14: 589-595.
43. Kant S, Bromberg J, Haas M, Brennan D. Donor-derived cell-free DNA and the prediction of BK virus-associated nephropathy. Transplant Direct. 2020; 6: e622.
44. Kant S, Brennan DC. Donor derived cell free DNA in kidney transplantation: The circa 2020-2021 update. Transpl Int. 2022; 35: 10448.
45. Drachenberg CB, Papadimitriou JC. Polyomavirus-associated nephropathy: Update in diagnosis. Transpl Infect Dis. 2006; 8: 68-75.

46. Nickeleit V, Singh HK, Randhawa P, Drachenberg CB, Bhatnagar R, Bracamonte E, et al. The Banff Working Group classification of definitive polyomavirus nephropathy: Morphologic definitions and clinical correlations. J Am Soc Nephrol. 2018; 29: 680-693.
47. Bouatou Y, Nguyen TQ, Roelofs JJ, Bemelman FJ, Michielsen L, Goldschmeding R, et al. A multicenter application of the 2018 Banff classification for BK polyomavirus-associated nephropathy in renal transplantation. Transplantation. 2019; 103: 2692-2700.
48. Nickeleit V, Hirsch HH, Zeiler M, Gudat F, Prince O, Thiel G, et al. BK-virus nephropathy in renal transplants-tubular necrosis, MHC-class II expression and rejection in a puzzling game. Nephrol Dial Transplant. 2000; 15: 324-332.
49. Hirsch HH, Brennan DC, Drachenberg CB, Ginevri F, Gordon J, Limaye AP, et al. Polyomavirus-associated nephropathy in renal transplantation: Interdisciplinary analyses and recommendations. Transplantation. 2005; 79: 1277-1286.
50. Singh HK, Andreoni KA, Madden V, True K, Detwiler R, Weck K, et al. Presence of urinary Haufen accurately predicts polyomavirus nephropathy. J Am Soc Nephrol. 2009; 20: 416-427.
51. 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: 1057-1070.
52. Sood P, Senanayake S, Sujeet K, Medipalli R, Zhu YR, Johnson CP, et al. Management and outcome of BK viremia in renal transplant recipients: A prospective single-center study. Transplantation. 2012; 94: 814-821.
53. Kable K, Davies CD, O'connell PJ, Chapman JR, Nankivell BJ. Clearance of BK virus nephropathy by combination antiviral therapy with intravenous immunoglobulin. Transplant Direct. 2017; 3: e142.
54. Sharma AP, Moussa M, Casier S, Rehman F, Filler G, Grimmer J. Intravenous immunoglobulin as rescue therapy for BK virus nephropathy. Pediatr Transplant. 2009; 13: 123-129.
55. 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: 394.
56. Benotmane I, Solis M, Velay A, Cognard N, Olagne J, Gautier Vargas G, et al. Intravenous immunoglobulin as a preventive strategy against BK virus viremia and BKV-associated nephropathy in kidney transplant recipients-Results from a proof-of-concept study. Am J Transplant. 2021; 21: 329-337.
57. Josephson MA, Gillen D, Javaid B, Kadambi P, Meehan S, Foster P, et al. Treatment of renal allograft polyoma BK virus infection with leflunomide. Transplantation. 2006; 81: 704-710.
58. Krisl JC, Taber DJ, Pilch N, Chavin K, Bratton C, Thomas B, et al. Leflunomide efficacy and pharmacodynamics for the treatment of BK viral infection. Clin J Am Soc Nephrol. 2012; 7: 1003-1009.
59. Faguer S, Hirsch HH, Kamar N, Guilbeau-Frugier C, Ribes D, Guitard J, et al. Leflunomide treatment for polyomavirus BK-associated nephropathy after kidney transplantation. Transpl Int. 2007; 20: 962-969.
60. Guasch A, Roy-Chaudhury P, Woodle ES, Fitzsimmons W, Holman J, First MR, et al. Assessment of efficacy and safety of FK778 in comparison with standard care in renal transplant recipients with untreated BK nephropathy. Transplantation. 2010; 90: 891-897.

61. Lee BT, Gabardi S, Grafals M, Hofmann RM, Akalin E, Aljanabi A, et al. Efficacy of levofloxacin in the treatment of BK viremia: A multicenter, double-blinded, randomized, placebo-controlled trial. Clin J Am Soc Nephrol. 2014; 9: 583-589.
62. Knoll GA, Humar A, Fergusson D, Johnston O, House AA, Kim SJ, et al. Levofloxacin for BK virus prophylaxis following kidney transplantation: A randomized clinical trial. JAMA. 2014; 312: 2106-2114.
63. Vats A, Shapiro R, Randhawa PS, Scantlebury V, Tuzuner A, Saxena M, et al. Quantitative viral load monitoring and cidofovir therapy for the management of BK virus-associated nephropathy in children and adults. Transplantation. 2003; 75: 105-112.
64. Keller LS, Peh CA, Nolan J, Bannister KM, Clarkson AR, Faull RJ. BK transplant nephropathy successfully treated with cidofovir. Nephrol Dial Transplant. 2003; 18: 1013-1014.
65. Schold JD, Rehman S, Kayler LK, Magliocca J, Srinivas TR, Meier-Kriesche HU. Treatment for BK virus: Incidence, risk factors and outcomes for kidney transplant recipients in the United States. Transpl Int. 2009; 22: 626-634.
66. Sawinski D, Forde KA, Trofe-Clark J, Patel P, Olivera B, Goral S, et al. Persistent BK viremia does not increase intermediate-term graft loss but is associated with de novo donor-specific antibodies. J Am Soc Nephrol. 2015; 26: 966-975.
67. Hardinger KL, Koch MJ, Bohl DJ, Storch GA, Brennan DC. BK-virus and the impact of pre-emptive immunosuppression reduction: 5-year results. Am J Transplant. 2010; 10: 407-415.
68. Geetha D, Sozio SM, Ghanta M, Josephson M, Shapiro R, Dadhania D, et al. Results of repeat renal transplantation after graft loss from BK virus nephropathy. Transplantation. 2011; 92: 781-786.
69. Womer KL, Meier-Kriesche HU, Patton PR, Dibadj K, Bucci CM, Foley D, et al. Preemptive retransplantation for BK virus nephropathy: Successful outcome despite active viremia. Am J Transplant. 2006; 6: 209-213.
70. Leeaphorn N, Thongprayoon C, Chon WJ, Cummings LS, Mao MA, Cheungpasitporn W. Outcomes of kidney retransplantation after graft loss as a result of BK virus nephropathy in the era of newer immunosuppressant agents. Am J Transplant. 2020; 20: 1334-1340.