Management of BK Polyomavirus Infection in Kidney and Kidney-Pancreas Transplant Recipients

A Review Article

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KEYWORDS

• Kidney transplantation • BK virus • BKV-associated nephropathy (BKVAN)
• Polyomavirus

KEY POINTS

- BK virus (BKV) infection is common in kidney transplant recipients.
- BKV-associated nephropathy can cause premature graft loss in severe cases.
- Preventive strategy with active surveillance has improved outcomes of BKV infection but optimal management and specific therapy remain unclear and variable.
- Judicious immunosuppression adjustment is warranted in case of significant BK viremia and nephropathy.
- Currently, there is a limited role of use of antiviral agents either as prophylaxis or active treatment.

HISTORY AND BACKGROUND

BK virus (BKV) belongs to a large family called Polyomaviruses. Polyma in the Greek language means many (-poly) tumors (-oma). There are 77 recognized species in this family. Of these, 13 species, which are ubiquitous and usually asymptomatic, are known to infect humans.[1] However, 4 species of polyomaviruses are associated

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with human diseases: BKV[2]; JC virus (JCV)[3]; Merkel cell virus[4]; and, most recently, New Jersey polyomavirus.[5]

JCV and BKV are 70% related in their genome sequence. JCV was first discovered in 1959[6] but it was not until 1971 that it was isolated from a brain of a patient with Hodgkin disease diagnosed with progressive multifocal leukoencephalopathy.[7] The same year and in the same issue of the *Lancet*, BKV was first described.[8]

BK Virus is named after a Sudanese patient who suffered from endstage renal disease secondary to chronic pyelonephritis and underwent a living-related kidney transplant. Postoperative course was complicated with 2 mild rejections. Five months after transplant, the patient was admitted with graft dysfunction and ureteric obstruction. Tissue culture from the donor's ureter revealed a virus with unique cytopathic effect that distinguished the newly discovered virus from the rest of the polyoma viruses.[8]

EPIDEMIOLOGY AND ROUTE OF TRANSMISSION

There have been 4 genotypes identified for BKV (I to IV). BKV type I has the higher prevalence in the 4 groups. Baksh and colleagues[9] described 19 cases of renal allograft viral interstitial nephritis due to BKV. Eleven out of the 19 grafts (58%) corresponded to genotype I. Interestingly, in addition to BKV, JCV was seen in 7 interstitial nephritis grafts (37%), suggesting that both JCV and BKV can be isolated from renal tissue. This is consistent with some case reports linking JCV with a milder form of nephropathy seen in renal transplant patients.[10–12]

BKV is ubiquitous, with a worldwide seroprevalence in adults of 75% (range 46%–94%)[13] and of 30% to 90%.in the United States and Europe.[14,15] In several anecdotal reports, 60% to 100% of children are seropositive to BKV by the age of 10 years, indicating that infection occurs early in life and is usually asymptomatic.[16] The antibodies then decline to around 70% as age advances[17]; this observation suggests the role of maternal fetal antibodies transmission, which is supported by the identification of BKV IgM in newborns[18] and BKV genome in aborted fetuses.[19] However, there is no evidence in the literature suggesting teratogenicity or adverse fetal events secondary to BKV prenatal transmission. Following primary infection, the virus remains latent in the renal epithelium (tubular, transitional, and parietal epithelium) due to its tropism to the urinary tract.

The route of BKV transmission is believed to be human-to-human with no animal reservoir identified. To date, there is no specific route of transmission that has been identified. Some reports have identified BKV in stool[20,21] and sewage,[22] suggesting a possible fecal-oral route. Other studies detected BKV in tonsillar tissues,[23] which suggests either an oral or a respiratory route of transmission might be possible, with the latter the most important.

CLINICAL SIGNIFICANCE AND PREVALENCE AFTER KIDNEY AND KIDNEY-PANCREAS TRANSPLANTATION

BK Virus in Immunocompetent Population

As previously mentioned, BKV is highly seroprevalent in the healthy immunocompetent population, mostly presenting as asymptomatic low-grade viruria with no data suggesting clinical significance. Coleman and colleagues[24] showed evidence of high incidence of asymptomatic BKV viruria among 1235 pregnant women, which was attributed to impaired cell-mediated immunity, with no evidence of subsequent complications or fetal transmission.

BK Virus in Immunocompromised Population

BKV is reported to be pathogenic in the immunocompromised population mainly among patients with transplants. Interestingly, among kidney and kidney-pancreas transplantation patients, BKV reactivation primarily causes tubulointerstitial nephritides known as BKV-associated nephropathy (BKVAN) and ureteral stenosis.[25] On the other hand, BKV reactivation in allogeneic hematopoietic cell transplantation primarily causes hemorrhagic cystitis, which is rarely observed in the kidney transplant population.[26] BKVAN in native kidneys after nonkidney organ transplantation is rarely reported, even in settings of the same degree of immunosuppression.[27] This observation suggests that factors associated with the process of kidney transplantation might play a role, such as ischemia-reperfusion injury, and tissue trauma that might activate the latent virus in the donated kidney; therefore, donor–recipient transmission can be supported. Bohl and colleagues[28] demonstrated the homology of the BKV capsid component viral protein 1 by performing polymerase chain reaction (PCR) of BKV in donor–recipient pairs to suggest that BKV is derived from the donor.

Course of BK Virus Reactivation

Previous reports have described that the course of the BKV disease spectrum among the kidney and kidney-pancreas transplant population evolves from reactivation of the latent BKV in the urinary tract epithelium and manifests as BK viruria; to BK viremia; to BKVAN; to graft dysfunction, "which is the most common clinical presentation in this population"; to, eventually, graft failure.[29–31]

BK Virus and Graft Rejection

It is strongly believed that the main mechanism of graft dysfunction after BKV reactivation is related to the direct cytopathic injury caused by viral invasion. Another proposed mechanism is that decreased immunosuppressive medication after BKV reactivation might induce rejection.[32] Recently, Sawinski and colleagues[33] reported a novel association between BKV and the development of de novo donor-specific antibodies and subsequent graft rejection owing to an allosensitization effect induced by changing in the net immunosuppression state from over-immunosuppression to under-immunosuppression after reduction in immunosuppression medication.

BK Virus and Malignancy

As the name of the family, polyoma, or many tumors, implies (as suggested in the literature), there might be a link between BKV and malignancy, especially in prostate cancer and bladder cancer. Monini and colleagues[34] identified BKV particles in normal and neoplastic tissue samples of prostatic cancer by DNA PCR. Interestingly, the DNA load was significantly higher in neoplastic tissue compared with normal tissue, ruling out the possibility that detection of the virus from the malignant tissues was due to the ubiquitous presence of BKV. Conversely, Keller and colleagues[35] reported BKV seropositive status was associated with better prognosis in 226 subjects with prostate cancer, owing to beneficial immune response. Similar controversy is reported regarding the possible association of BKV and bladder cancer.[36,37] There is no definitive association between BKV and malignancy in humans.[38]

Risk Factors for BK Virus Reactivation and BK Virus–Associated Nephropathy

The literature is inconsistent concerning the risk factors for BKV. **Table 1** summarizes the reported risk factors of BKV reactivation and BKVAN.[25,30–33]

Table 1
Risk factors of BK virus reactivation and BK virus–associated nephropathy

Risk Factors of BKV Reactivation After Transplantation		
Recipient-Related	**Donor-Related**	**Transplant-Related**
• Older age • Male gender • Steroid exposure • Antirejection treatment • Diabetes mellitus • Negative BKV serostatus	• Female gender • African American • Deceased donors • BKV seropositive status	• High immunosuppression drug levels • Use of tacrolimus • Thymoglobulin induction • Ureteral stents • HLA mismatch • A,B, OR O blood groups incompatibility • Ischemia or reperfusion injury • Long ischemia time

In a prospective study that included 240 kidney-only transplant recipients, Sood and colleagues[39] reported African American recipients to be protected against BKV reactivation. A recent retrospective study, which included 573 kidney and kidney-pancreas transplant cases, identified vitamin D insufficiency (25-hydroxvitmain D <30 ng/mL) to be an independent risk factor for infections, including BKV reactivation, after adjusting for the degree of immunosuppression in a logistic regression model.[40]

We previously reported that cytomegalovirus (CMV) reactivation after kidney transplantation might be protective against BKV reactivation, possibly due to decreased immunosuppression after CMV infection is identified.[41]

The key element for the risk and pathogenesis of BKV reactivation is believed to be the imbalance between the BKV replication and BKV- specific immunity.[2] As previously mentioned, risk factors of BKV are inconsistent among various studies. However, it is clear that the degree of immunosuppression is the strongest risk factor for BKV reactivation. This fact caused some investigators to consider that BKV reactivation may be a marker for over-immunosuppression.[42] Brennan and colleagues[43] evaluated the incidence of BKV reactivation with 4 different immunosuppressive regimens in a prospective study that included 200 subjects after kidney transplantation. The subjects were randomly assigned to receive tacrolimus (n = 134) or cyclosporine (n = 66). As a second immunosuppression agent, azathioprine (n = 112) was used. Mycophenolate mofetil (MMF) (n = 88) was used instead of azathioprine under certain circumstances (eg, second transplant, panel reactive antibody >20%) and all subjects received prednisone tapered by month 3 to 5 to 7.5 mg daily. By year 1, their study revealed no difference in the rate of BK viruria or viremia among those receiving tacrolimus compared with cyclosporine. In addition, no differences were found with azathioprine compared with MMF. Although there is no definitive single immunosuppressive medication or specific combination that has been confirmed to be associated with BKV reactivation, Hirsch and colleagues[44] recently reported that the mammalian target of rapamycin (mTOR) inhibitor sirolimus can inhibit BKV replication during early gene expression, supporting the notion that BKV replication depends on mTOR activity. Calcineurin inhibitor (CNI) cyclosporine A also inhibited BKV replication. On the other hand, tacrolimus was reported as an enhancer to BKV replication; moreover, it reversed the sirolimus inhibition effect. These findings definitely open new horizons for clinical trials aiming to find a specific anti-BKV drug and provide guidance for modifying immunosuppressive medications in patients with BK viremia.

Low Versus High BK Viremia

In agreement with other studies, the authors previously reported that BK viral loads less than 10,000 copies/mL were not associated with graft adverse effects at 3, 6, or 12 months posttransplant, increased graft rejection rate, or increased risk of BKVAN when compared with BKV-negative transplant recipients.[45–49] Moreover, spontaneous clearance rate in the low viremia population was reported to be as high as 95% without intervention or change in the immunosuppression protocol, suggesting that close observation might be a reasonable option for those patients.[45] On the other hand, BK viral loads greater than 10,000 copies/mL were reported to be the cutoff for significant BK viremia and subsequent negative outcomes, including graft dysfunction, graft rejection, and development of BKVAN, which mandates immediate intervention.[46–48] Indeed, recent reports support that a plasma PCR viral load greater than 10,000 copies/mL for greater than 3 weeks is a surrogate marker for presumptive BKVAN.[47–49]

DIAGNOSIS

The prevalence of BK viremia among the kidney and kidney-pancreas transplant population has been reported to range from 7% to 27%,[46–48] with most cases observed during the first year particularly, as early as 2 to 6 months posttransplant.[49] The incidence of BKVAN in several reports ranged between 1% to 27%, depending on the surveillance protocol, and possible early detection and intervention of BKV reactivation before graft injury occurs.[44–49] Owing to better awareness of the BKV and its adverse effect on renal graft outcome, the incidence of graft loss due to BKVAN has significantly declined over the past 20 years.[25,50]

BKV infection is almost always asymptomatic and only manifests as a functional impairment of kidney transplant. Active replication of BKV in the urinary tract occurs before renal function impairment; hence transplant centers now routinely use screening methods for early detection.

Screening Protocols

Screening can be performed by 1 of 3 ways:

1. Decoy cells: First described by Coleman and colleagues,[51] these are urothelial cells with characteristic large basophilic nuclear inclusions that can be identified by urine cytology. Presence of these in urine is suggestive of BK viral replication.[52]
2. BK viruria: Genomic detection and quantification in urine, by PCR technique.
3. BK viremia: Genomic detection and quantification in blood, again, by PCR technique.

In North America, quantitative plasma BKV PCR measurement is the preferred screening method. Urine cytology (decoy cells) and urine BKV PCR are not commonly used. As previously mentioned, the initial process of BKV infection in renal transplant recipients is BK viruria; however, two-thirds of patients with BK viruria do not develop either viremia or BKVAN. This reflects the low positive predictive value of BK viruria. In summary, plasma BKV PCR is the preferred method.

Nevertheless, the quantification of BK viral load should be interpreted with caution because of interassay variation. To standardize quantitative BK viral load testing, the World Health Organization (WHO) proposed an international standard for BKV PCR.[53] This initiative is expected to enhance clinical research focusing on BKV management.

Utility of these screening methods has been extensively investigated. **Table 2** summarizes sensitivities and specificities, and advantages and disadvantages of each screening method.

Table 2
Utility of BK virus screening methods

Method	Utility	Sensitivity[a]	Specificity[a]	PPV[a]	NPV[a]	Disadvantage	Advantage
1. Urine							
Decoy Cells Qualitative PCR Quantitative PCR	++ + +++	100%	45%	Low	High	• Decoy cells identification needs experience • Not to monitor decline in viral load after decrease immunosuppression due to delayed response	• Less cost • Precedes BK viremia by 6–12 wk and flags patients who require intervention and intensive screening by plasma PCR
2. Plasma							
Qualitative PCR Quantitative PCR	+ ++++	100%	66%[b]	High	Low	• Expensive • May progress to BKVAN quickly, with a window period of only 2 wk	• High PPV • Immediate response to reduction in immunosuppression

+ Scale 1 to 4: + not commonly used, ++++ very commonly used.
Abbreviations: NPV, negative predictive value; PPV, positive predictive value.
[a] For detecting BKV reactivation.
[b] Specificity increases to 90% if viral load is greater than 10,000 copies/mL of blood.

Frequency of surveillance varies from center to center but most commonly, including in University Hospitals, is done during months 1, 3, 6, 9, and 12 of the first year posttransplant, then for cause when unexplained graft dysfunction is noticed. Because this frequency might occasionally miss early stages of BK viremia, some centers screen monthly for the first 6 months, then every other month until 1 year, quarterly for the second year, then as clinically indicated afterward.[54] According to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines and the American Society of Transplantation recommendations, options include (1) monthly screening with quantitative plasma BKV PCR test for the first 3 to 6 months, followed by every 3 months until 24 months after transplant; or (2) biweekly urine tests (BKV PCR or cytology), followed by a quantitative plasma PCR test, if positive, for the first 3 months, then monthly until month 6, and then every 3 months until 24 months after transplant.[55]

Kidney Biopsy

Although the diagnosis of presumptive BKVAN can be made based on a quantitative plasma BK viral load greater than 10,000 copies/mL,[56] kidney biopsy remains the gold standard to diagnose definitive BKVAN.[2] However, early BKV infection can be limited to focal areas and easily missed. Indeed, discordance of histologic findings was observed in up to 37% of simultaneously obtained biopsy tissue cores.[57] Virus-infected atypical tubular cells can be prominent but additional virus staining should be sought to safely differentiate BKVAN from acute rejection, which resembles it morphologically (**Fig. 1**). Simian virus 40 is widely used and in situ hybridization of BKV can be applied if necessary.[58]

TREATMENT

Reduction of immunosuppression is the mainstay of treatment of persistent BK viremia and/or biopsy-proven BKVAN. Reduction is done carefully in a stepwise manner while closely monitoring quantitative plasma BKV PCR and serum creatinine, generally every 2 weeks. Opinions regarding which immunosuppressive drug to be withdrawn first are variable. One strategy is to first reduce CNI (tacrolimus or cyclosporine) dosing in a stepwise manner until discontinuation. Another strategy is to first

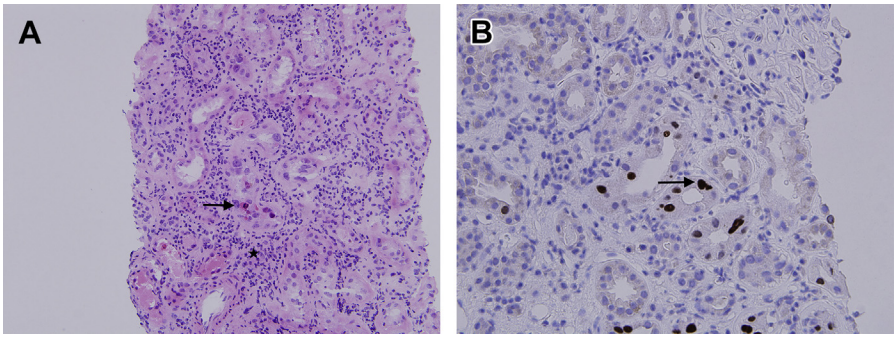

Fig. 1. (*A*) Hematoxylin-eosin (H&E) stain of renal biopsy showing positive tubular cells viral inclusions and interstitial inflammation. Tubular epithelial cells with cytopathic changes due to BK inclusions (*black arrow*). Interstitial inflammation (*black star*). (*B*) Immunohistochemical stain of renal biopsy showing positive staining for the BK T antigen. Tubular epithelial cells showing viral inclusions that are positive for simian virus 40 antigen by immunohistochemistry (*arrow*).

reduce the antiproliferative drugs (mycophenolate, azathioprine, sirolimus) in a stepwise manner of 50% each step, until discontinuation. Sometimes, if BK viremia persists at a high level of greater than 10, 000 copies/mL even after discontinuation of 1 drug, reduction of another drug is needed. Due to the lack of an objective testing that can measure an individual's immunity level against the development of BKVAN, and because different individuals have different immunosuppression responses, reduction in immunosuppression is done arbitrarily while monitoring BK viral load. At our center, we occasionally withdrew both CNI and antiproliferative drugs until downtrend in BK viremia was achieved (**Fig. 2**). In such circumstances, when rejection becomes of concern due to under-immunosuppression, other options might be sought. Alternatively, switching from tacrolimus to cyclosporine is embraced at some institutions.[59]

Alternative to the standard CNI regimen, belatacept was approved by the US Food Drug Administration in June 2011. There are limited data regarding BKV infection with belatacept use. The maintenance dose of belatacept is administered parentally. In contrast to CNI, dose adjustment is not typically required. In cases of BKV reactivation with belatacept regimen, reduction or withdrawal of antiproliferative drugs is the first step to manage BKV infection; however, the proper measure to adjust maintenance belatacept dose has not been studied. The frequency of belatacept is typically extended to every 6 weeks instead of the routine 4 weeks if further reduction of immunosuppression medication is warranted, although this lacks evidence.[60]

Leflunomide

Leflunomide is a prodrug whose active metabolite, teriflunomide A77 1726, inhibits dihydroorotate dehydrogenase, a key enzyme in the pyrimidine synthesis pathway of BKV replication, and tyrosine kinase. The inhibition of these enzymes leads to reduction in BK large T antigen expression and DNA replication.[61] In vitro studies have shown antipolyomavirus activity and clearance of BK viremia[62,63] but recent reports that studied the correlation between leflunomide usage and A77 1726 levels with BKV clearance has shown no significant benefit of its use in clearing BK viremia.[64] This drug has fallen out of favor, at least at the United States, due to limited efficacy and side effects, mainly neuropathy, lethargy, gastrointestinal intolerance, and loss of taste without any correlation to plasma concentration. Because leflunomide has some immunosuppressive activity, its use might be considered in conjunction with reduced does of immunosuppressive regiments. When used, the loading dose of leflunomide is 100 mg daily for 3 to 5 days, followed by maintenance at 20 to 60 mg daily, aiming for target leflunomide trough levels of 40 to 80 mg/dL. Without a loading dose, leflunomide might take up to 2 months to reach its target levels; hence, it is not expected to cause a rapid effect on viral clearance.[65] Pregnancy is a contraindication for receiving leflunomide owing to its reported teratogenicity, and elimination of the drug from the circulation might take up to several months owing to long half-life.[66] If major toxicity or unplanned pregnancy occurs, a washout procedure is undertaken with oral cholestyramine (typically 8 g 3 times daily for 11 days) or activated charcoal. Teriflunomide cannot be removed by dialysis; therefore, hemodialysis is not a treatment approach for patients who are experiencing major toxicity or who have taken an overdose of leflunomide.

Cidofovir and Brincidofovir

Cidofovir has modest in vitro activity against polyomaviruses by an unclear mechanism.[59] Several case reports have claimed its efficacy as an adjunctive treatment of

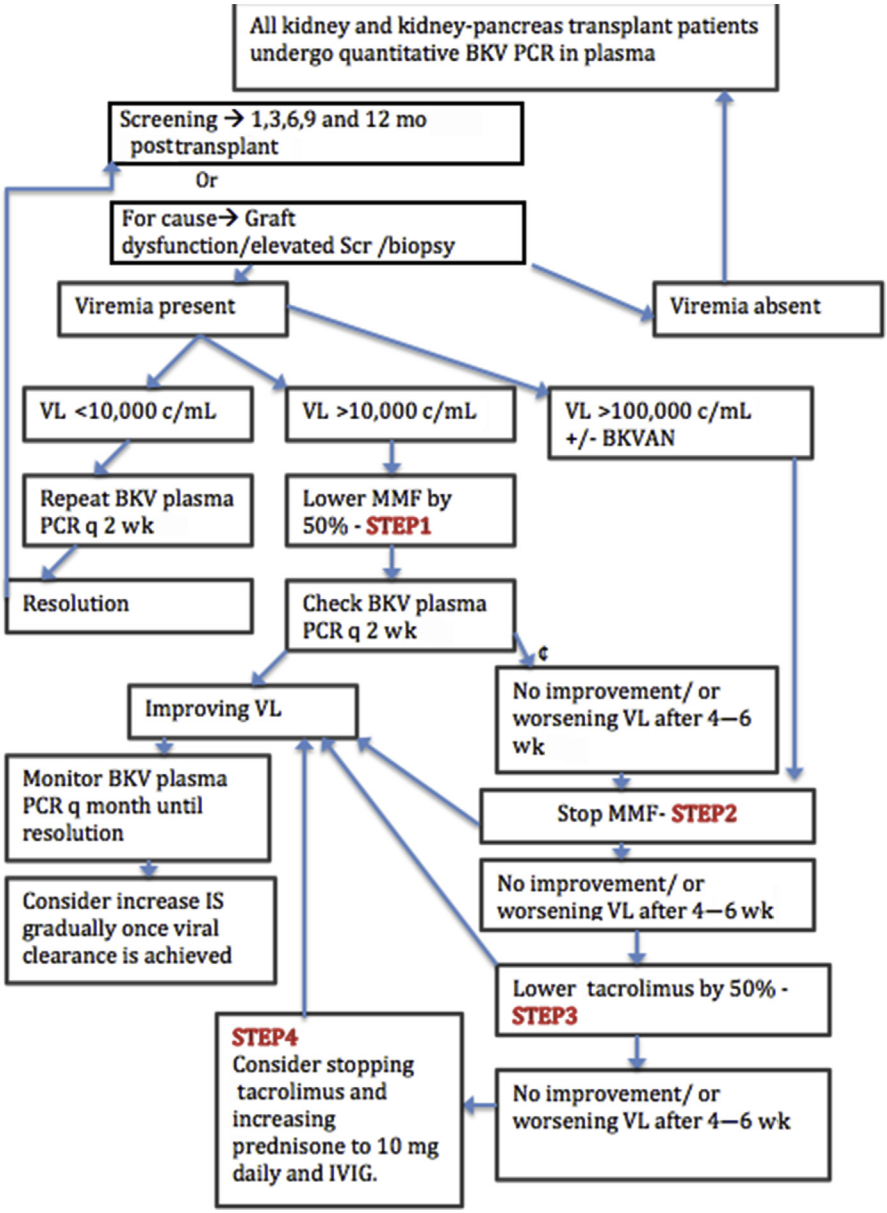

Fig. 2. Treatment algorithm. C, copies; IS, immunosuppression medications; IVIG, intravenous immunoglobulin; q, every; Scr, serum creatinine; VL, viral load. (*Courtesy of* Kidney and Kidney-Pancreas program at University Hospitals, Cleveland Medical Center, Cleveland, OH; with permission.)

BK viremia or BKVAN. A retrospective review by Kuten and colleagues,[67] including 75 kidney and kidney-pancreas recipients ascribed preservation of graft function to cidofovir usage in conjunction with reduced immunosuppression. This favorable result was not appreciated in older recipients with higher BK viral loads. Cidofovir dosage is

1 mg/kg induction and 0.5 mg/kg maintenance every 2 weeks. Major side effects include nephrotoxicity and acute uveitis. Many centers do not use cidofovir at all.

Brincidofovir is the prodrug and lipid-ester formulation of cidofovir (ie, CMX001). Some case reports suggested its use in pediatric renal transplant population, which seems well-tolerated except for diarrhea; however, it lacks randomized controlled trial (RCT) data and further scientific data are warranted.[68] Trials in hematopoietic stem cell transplantation have been halted owing to high graft-versus-host disease–related mortality; and no research is currently ongoing.

Intravenous Immunoglobulin

Similar to other conditions that respond to intravenous immunoglobulin (IVIG), the exact mechanism of action in BKV management remains unclear; however, a detection of BKV-neutralizing antibodies in IVIG preparation was reported.[69] Vu and colleagues[70] reported the efficacy of IVIG administered to 30 kidney transplant recipients after reduction in immunosuppression and leflunomide failed to decrease BK viremia after 8 weeks. Following IVIG administration, 90% of subjects had a decrease in viremia. Although IVIG is not routinely used at university hospitals, the safety and ease of administration of IVIG is encouraging. Occasionally use IVIG in cases of persistent BK viremia after reduction of immunosuppression, and when BK viremia occurred with or after an episode of antibody-mediated rejection. Several limitations apply when interpreting the literature claiming the efficacy of IVIG in clearing BK viremia or BKVAN. RCTs are warranted to prove the efficacy of this intervention. When used, the dose of IVIG is 1 to 2 g/kg divided over 2 to 5 days.

Fluoroquinolones Use as Prophylaxis and Adjunctive Therapy

Fluoroquinolones (FQs) are broad-spectrum antimicrobial agents that inhibit bacterial topoisomerase II and IV, and are widely used in clinical practice. In vitro, FQs interfere with helicase activity of BKV large T antigen protein, which is essential for viral replication.[71] One retrospective study showed a potential benefit of prophylactic ciprofloxacin use in reduction of early BKV infection.[72] Currently, an RCT is ongoing to prove efficacy of prophylactic ciprofloxacin use in BKV infection in renal transplant recipients (ClinicalTrials.gov identifier: NCT01789203). Nonetheless, 3-month levofloxacin use did not reduce the incidence of BK viruria (levofloxacin group 29% vs placebo group 33%, $P > .05$) in a prospective study that was stopped early owing to lack of funding.[73] Furthermore, there was a significantly higher rate of levofloxacin-resistant bacterial organisms isolated (relative risk 1.75, 95% CI 1.01–2.98), which substantially affects the outpatient treatment strategy for common urinary tract infections caused by Enterobacteriaceae and *Pseudomonas aeruginosa*. Levofloxacin at 500 mg daily was tested as adjunctive therapy for BK viremia in a different RCT.[74] There was no statistical difference in plasma BK viral load during the study period, up to 6 months. A recent report studied effect of 3 months of ciprofloxacin in a group of 29 kidney transplant recipients compared with matched 43 control subjects. Ciprofloxacin prophylaxis showed no difference in the incidence of BK infection.[75] In conclusion, there is no current recommendation regarding the usage of FQs as a prophylactic or adjunctive treatment of BKV reactivation after kidney transplantation.

Retransplantation after BK Virus–Associated Nephropathy Graft Loss

As previously mentioned, graft loss due to BKVAN has been significantly declining over the last 2 decades owing to understanding of the disease process and improvement in its management; however, retransplantation after graft loss from BKVAN remains a challenge for transplant physicians. A history of BKVAN does not preclude

another transplant candidacy. An analyses of United Network for Organ Sharing and Organ Procurement Transplant Network database reported a general acceptance and favorable results of retransplantation after BKVAN graft loss, although it requires special considerations.[76] Retransplantation is recommended after BK viremia clearance to decrease risk of BKVAN in the retransplanted kidney.[77] Nephrectomy of prior failed allograft if BK viremia persists despite minimization of immunosuppression remains controversial with no supporting evidence. The key to successful retransplantation is balance of overall immunosuppression, risk of BKV replication, and risk of rejection.

SUMMARY

BKV is the most common opportunistic viral infection encountered in kidney allografts and high viral load can lead to graft failure. Fortunately, due to effective preemptive monitoring and early reduction of immunosuppressive medication, graft failure due to BKVAN has decreased considerably. Owing to the unproven efficacy of antiviral drugs against BK, reduction in immunosuppression is the only effective measure in the treatment of this complication; however, protocols of reduction in immunosuppression vary among institutions and can be very challenging due to the risk of subsequent rejection.

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