

## NARRATIVE REVIEW

# Polyomavirus Nephropathy: A Current Perspective and Clinical Considerations

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During the last decade, the human polyomaviruses (BK virus and, much less commonly, JC virus) have entered the realm of routine clinical decision making for providers caring for kidney transplant recipients. The emergence of polyomavirus-associated nephropathy (PVAN) as an important clinical entity coincided with the development and use of more potent immunosuppression agents, currently the only clear risk factor for reactivation of the virus. Ongoing efforts to define the pathogenesis, clinical presentation, and appropriate management of PVAN have led to a greater ability to prevent and control viral-induced interstitial nephritis despite continued deficiencies in our understanding of risk factors for disease and lack of published prospective polyomavirus-specific antiviral trials. The purpose of this review is to summarize advances made during the last decade and highlight emerging data that address common clinical considerations the clinician currently faces in the understanding and management of PVAN.

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**INDEX WORDS:** Polyomavirus; BK virus; kidney transplantation; review.

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As immunosuppression for kidney transplantation has grown from its roots of corticosteroids and azathioprine to a wider array of more potent agents, the epidemiological characteristics and severity of opportunistic and unusual infections have expanded. Most overtly, and perhaps most importantly, polyomavirus-associated nephropathy (PVAN) has become a major cause of kidney dysfunction and graft loss since the 1990s. First described in 1971,<sup>1</sup> but largely unnoticed during the following decades, PVAN reappeared in the kidney transplantation literature in the late 1990s as a potential cause of graft injury.<sup>2-4</sup> In early reports, the diagnosis of PVAN carried a poor prognosis, with more than 50% of patients with PVAN experiencing graft dysfunction and premature graft loss.<sup>5</sup> Now, after almost a decade of heightened investigation and clinical experience, the transplantation and nephrology community has better described the entity of PVAN, its natural history, and measures to prevent graft loss. The purpose of this review is to synthesize our present knowledge of PVAN and address questions that frequently arise in the understanding and management of the disease.

### PREVALENCE AND CLINICAL MANIFESTATIONS

Polyomaviruses are a family of DNA viruses that include the human pathogens JC virus and BK virus and the primate pathogens simian virus

40 (SV40) and monkey polyomavirus, which are tropic to renal tubular epithelial cells. Other human polyomaviruses have been identified (KI, WU, and MCV),<sup>6</sup> but without association with nephropathy. In humans, primary infection typically occurs in childhood, commonly presenting as a respiratory viral infection. After infection, the polyomaviruses establish latency in tubular epithelial cells of the kidney without untoward effects until states of immune incompetence or suppression permit transition from latent to lytic phases. Overall, the seroprevalence indicative of prior infection in the general population is approximately 80%.<sup>7</sup> JC virus has been described best in patients with later-stage acquired immunodeficiency syndrome (AIDS), typically presenting as progressive multifocal leukoencephalopathy, a condition that is gaining increased attention in the transplantation community with recent

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warnings of an association with mycophenolate mofetil (MMF) use.<sup>8</sup> BK virus reactivation is described predominantly as an interstitial nephritis in kidney transplant recipients. Clinical presentations of BK virus reactivation in kidney transplant recipients most commonly are asymptomatic deterioration in kidney function, but reports of ureteral stricture<sup>9</sup> and hemorrhagic cystitis<sup>10</sup> as initial presentations of infection also have been reported.

In kidney transplant recipients, BK virus reactivation occurs soon after transplantation and is identified in the urine of approximately 30% to 50% of patients at 3 months posttransplantation.<sup>11,12</sup> Progression from viruria to viremia occurs in approximately 10% to 15% of all kidney transplant recipients and is a harbinger of interstitial nephritis unless reductions in immunosuppression are made. Progression from viruria to viremia to nephropathy generally is accepted as a stepwise transition,<sup>5,11,13</sup> thus providing opportunity for screening strategies and early identification of patients at risk.

### DIAGNOSTIC TESTING FOR POLYOMAVIRUSES

Despite the availability of serological testing to identify prior exposure in donors and recipients, serological testing has not been helpful in predicting predisposition to disease (discussed later), and testing for polyomavirus relies primarily on evidence of viral replication in urine and blood (Table 1) and confirmatory histological examination. Identification of viruria can be performed by using a number of methods. Urinalysis with Papanicolaou staining for inclusion bodies in uroepithelial cells (termed decoy cells

because of appearance similar to malignant cells) is an effective means of early qualitative identification. Urine polymerase chain reaction (PCR) analysis for BK virus is more sensitive and has the added advantage of quantifying viral load, which may aid in predicting individuals at risk of progression to overt nephropathy. Less commonly, reverse-transcription PCR for BK virus RNA and electron microscopy for viral particles also have been described as potential diagnostic tests.<sup>5,14</sup> In general, detection of viruria is a sensitive, but not specific, marker for overt nephropathy. For example, the presence of urinary decoy cells carries a positive predictive value of approximately 20%,<sup>4,15</sup> and its assessment is operator dependent. Similar to urinalysis for decoy cells, the utility of urinary BK DNA testing has a high negative predictive value, but a poor positive predictive value.<sup>5,16</sup> If sustained and restricted to values that are significantly increased ( $>1 \times 10^7$  copies/mL), the positive predictive value may improve to 67%.<sup>17</sup>

Detection of viremia typically is performed by using quantitative PCR for DNA. In patients with BK virus-associated nephropathy (BKVAN), the viral copy number in blood generally is approximately 1/1,000 that found in urine. Viremia is seen in nearly 100% of patients with BKVAN, with a positive predictive value of approximately 60% because viremia is not always associated with histological identification of nephropathy (discussed later).<sup>11,17,18</sup>

#### Clinical Consideration No. 1: What Degree of BK Virus Viremia or Viruria Warrants Concern?

Given the consistent clinical progression from viruria to viremia to nephropathy, it has been suggested that viruria ( $>10^7$  viral copies/mL) or viremia ( $>10^4$  viral copies/mL) that persists for more than 3 weeks is adequate for the presumptive diagnosis of BKVAN,<sup>19</sup> although in the absence of a biopsy, this finding as a definitive diagnosis is not yet widely accepted.<sup>20</sup> A recent study compared the clinical utility of urinary decoy cells and quantitative urine and plasma BK virus PCR in detecting concurrent PVAN.<sup>21</sup> Comparing test results with findings on protocol biopsy, BK virus viremia greater than  $1.6 \times 10^4$  copies/mL had 100% sensitivity and 96% specificity, but only 50% positive predictive value for concurrent PVAN on biopsy, likely because of

**Table 1. Diagnostic Testing for BK Virus Nephropathy**

Test	Threshold Value	Correlation With PVAN on Biopsy
Decoy cells	$>10$ cells/cytospin	+
Urine BK virus DNA quantitative PCR	$>1 \times 10^7$ copies/mL	++
Blood/plasma BK virus DNA quantitative PCR	$>1 \times 10^4$ copies/mL	+++

Abbreviations: PCR, polymerase chain reaction; PVAN, polyomavirus-associated nephropathy.

the patchy nature of viral inclusion bodies and the potential to miss the diagnosis if medullary tissue is not obtained. BK virus viremia greater than  $2.5 \times 10^7$  copies/mL had 100% sensitivity, 92% specificity, and 31% predictive value, whereas urine decoy cells had 25% sensitivity, 84% specificity, and 5% positive predictive value. These values represent risks of concurrent BKVAN and thus lower threshold values should be used if the goal is to avoid the development of disease. One problem in defining a threshold value of viremia or viremia that may be predictive of PVAN on biopsy (or risk of development of PVAN) is that a number of different PCR assays with different primer and probe designs are available, which may lead to difficulty standardizing values.<sup>22</sup>

Given these limitations of noninvasive tests, kidney biopsy remains the gold standard for the diagnosis and management of BKVAN.<sup>20</sup> Histological findings on biopsy have been characterized and correlated with graft outcome<sup>23</sup> (Table 2), although these data may overestimate the rate of graft loss as current strategies lead to earlier diagnosis and management. Pattern A describes

early disease, with few cytopathic changes and minimal inflammation, tubular atrophy, and fibrosis. Pattern B describes greater degrees of inflammation, tubular atrophy, and fibrosis, further stratified to subpatterns B1, B2, and B3 to represent 10% to 25%, 25% to 50%, and greater than 50% injury. Pattern C describes end-stage PVAN, with a predominance of interstitial fibrosis and chronic inflammatory infiltrate and scant polyomavirus-staining cells. Because PVAN is tropic to the medulla, patchy in distribution,<sup>23</sup> and difficult to distinguish from acute rejection, at least 2 cores should be obtained with inclusion of medullary tissue for polyomavirus-specific histological analysis. Immunostaining results for polyomavirus cells can be falsely negative if monoclonal antibodies other than those directed against SV40 large T antigen (LTag) are used.<sup>24</sup>

#### Clinical Consideration No. 2: Does JC Virus Cause Nephropathy?

Given that most presentations of PVAN are associated with BK virus rather than JC virus, a number of investigators have proposed that the term PVAN be replaced with the term BKVAN and attention be focused specifically on screening and follow-up of BK virus. A prospective large single-center screening study<sup>25</sup> and various case reports<sup>26-28</sup> suggest that JC virus may rarely cause interstitial nephritis, with important differences in presentation. In the screening study, 980 patients were screened for urinary decoy cells during a 3-year period, 103 (13.8%) of whom had positive results and underwent urine and blood PCR analysis for both BK and JC virus, as well as kidney biopsy. By means of urine PCR, 56.3% were exclusively BK virus positive, 27.2% were exclusively JC virus positive, and 16.5% were positive for both. BK viremia was strongly associated with viremia (93.1% incidence), nephropathy on biopsy (51.7%), and subsequent graft dysfunction despite immunosuppression reduction (38%). In contrast, only 14.3% of JC-viruric patients were also viremic, whereas on biopsy, JC virus PVAN was diagnosed in 21.4% (6 of 28), with no patient experiencing clinical deterioration on follow-up. Interestingly, JC virus genomic sequences were identified in only 2 of these 6 patients, bringing into question the pathogenicity of JC virus. Thus, it appears that although JC virus may be identified in biopsy

**Table 2. Histological Patterns of Polyomavirus Nephropathy and Correlation With Graft Outcome**

Histological Pattern	Biopsy Description	Graft Loss (%)
a	Viral cytopathic changes in the epithelium of tubules	13
	Simian virus 40 <sup>+</sup> nuclear staining	13
	Minimal/no inflammation or tubular atrophy	
b	Viral cytopathic changes in epithelium of tubules	
	Simian virus 40 <sup>+</sup> nuclear staining	
	Interstitial inflammation and tubular atrophy:	
b1	<25% of core	40
b2	25%-50% of core	56
b3	>50% of core	78
c	Rare viral cytopathic changes in atrophic tubules	100
	Extensive tubular atrophy, chronic inflammation, and interstitial fibrosis	

*Note:* Simian virus 40<sup>+</sup> nuclear staining denotes signal on immunohistochemical staining with an antibody directed against simian virus 40 large T antigen.

Data from Drachenberg et al.<sup>23</sup>

**Table 3. Features of JC Versus BK Virus Nephropathy**

	JC Virus	BK Virus
Urinary viral shedding in healthy individuals	Up to 40%	0%-6%
Urinary viral shedding in kidney transplant recipients	30%-50%	30%-60%
Association with viremia	Rare	Common
Incidence of interstitial nephritis (PVAN) with graft dysfunction	Case report	1%-10%
Onset of nephropathy	Debatable, unpredictable from noninvasive studies	Stepwise progression from viruria to viremia to nephropathy

Abbreviation: PVAN, polyomavirus-associated nephropathy.

specimens, it is debatable whether it truly is a cause of interstitial nephritis or an epiphenomenon. If it is pathogenic, it is less common, less aggressive, and less overt in its histological footprint of SV40-positive tubular cells. Unfortunately, the high prevalence of asymptomatic JC virus shedding in urine in healthy adults<sup>29,30</sup> and the lack of correlation with viremia in immunosuppressed patients hinders the value of screening for JC virus, and most attention for screening and management appropriately has focused on BK virus (Table 3). In the setting of graft dysfunction with biopsy findings consistent with PVAN, but negative for BK virus serological markers, JC virus should be considered in the differential diagnosis.

### RISK FACTORS FOR THE DEVELOPMENT OF PVAN

Presently, the only widely accepted risk factor for the development of PVAN is degree of overall immunosuppression. Although high-dose tacrolimus and MMF immunosuppression have been associated with greater risk of developing PVAN in retrospective analyses,<sup>4,31</sup> 1 comparison of cyclosporine (CsA)- versus tacrolimus-based immunosuppression in combination with azathioprine in a prospective fashion did not implicate a specific agent in the development of viruria or viremia,<sup>11</sup> and PVAN has been described with every common immunosuppression regimen.<sup>32-34</sup> Prior treatment for acute rejection and treatment with lymphocyte-depleting agents also has been associated with increased risk of PVAN.<sup>5,35,36</sup> Additional proposed risk factors have been reported, including male sex, older age,<sup>37</sup> total HLA mismatches,<sup>5,35</sup> and deceased donor (versus living donor) transplantation,<sup>38</sup> but all have limited predictive value.

### Clinical Consideration No. 3: Should Serotyping of Donor and Recipient for BK Virus Immunoglobulin G Be Performed Routinely to Identify Patients at Risk of BKVAN, Similar to Current Cytomegalovirus-Monitoring Strategies?

Given that approximately 20% of the recipient population is seronegative for BKVAN at the time of transplantation, a reasonable hypothesis may be that these patients would form a group at high risk of development of BKVAN after transplantation of a kidney from a seropositive donor. However, pretransplantation serostatus in the recipient does not seem to be protective (if positive) or permissive (if negative) in either adults<sup>5,39</sup> or children.<sup>40</sup> However, analysis of the degree and type of seropositivity posttransplantation may become more clinically relevant. Increasing or high anti-BK immunoglobulin titers have been associated with more severe infection in an observational cohort<sup>41</sup> but clearance of virus in a treatment cohort,<sup>42</sup> whereas lower anti-BK virus immunoglobulin G and immunoglobulin A titers have been associated with increased risk of subsequent viremia.<sup>43</sup> Additionally, the immune response to BK virus is more complex than simply the formation of neutralizing antibodies because it appears that BK virus-specific T-cell responsiveness, specifically to VP1 and large T-antigen viral gene products, may be more important to the control of viral replication.<sup>44-47</sup>

Although serotyping of the recipient may be of low predictive value, serotyping of the donor may be of greater interest. Bohl et al<sup>39</sup> showed that as the donor BK virus antibody titer increases, risk of recipient viruria and viremia increases proportionately. An additional finding that HLA-C7 has a role in protection from BK

virus nephropathy<sup>39</sup> is of interest and deserves further study.

### TREATMENT OF ESTABLISHED PVAN

Given the absence of a proven polyomavirus-specific antiviral agent and the clear relationship of PVAN to immunosuppression burden, clinicians must first consider the primary treatment of patients with PVAN to be the judicious reduction of immunosuppression. Published descriptions of methods used to reduce immunosuppression vary primarily in the degree to which reduction is attempted. Ramos et al<sup>37</sup> described outcomes in 67 individuals with BKVAN in whom calcineurin inhibitor (CNI) exposure was decreased by 50%, with MMF discontinuation in 36 and MMF reduction in 14 patients. Graft failure after 12.6 months of follow-up was 16.4%. Vasudev et al<sup>38</sup> quantified the degree of immunosuppression reduction at diagnosis of BKVAN by using a point scale. After an approximately 40% reduction in overall immunosuppression and a 70% reduction in CNI exposure, 9 of 25 individuals experienced graft loss in a median follow-up of 8 months, with evidence that CNI reduction correlated with a slower rate of decrease in glomerular filtration rate. In a CNI/sirolimus (SRL)-based regimen, discontinuation of CNI with SRL/prednisone maintenance (goal SRL trough levels,  $10 \pm 3$  ng/mL), 5 of 9 patients lost graft function at a mean follow-up of 17.5 months.<sup>48</sup>

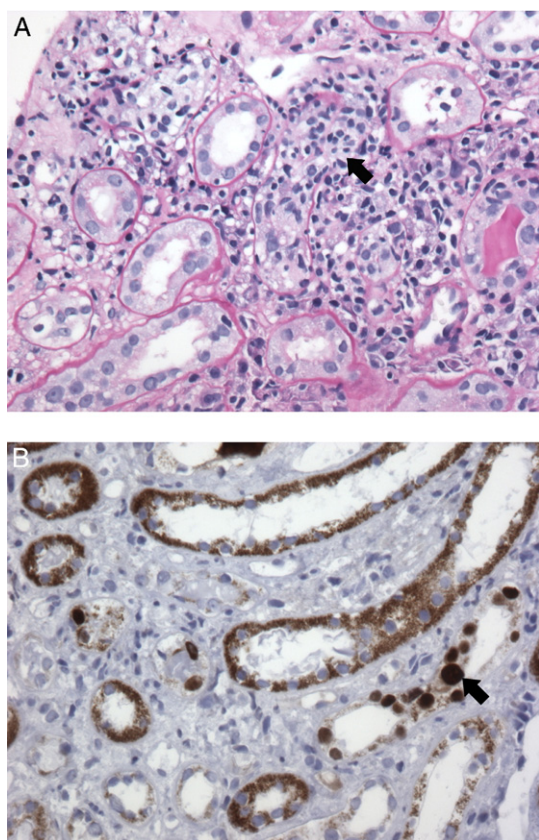
In none of these studies was there comparison of different immunosuppression reduction strategies. Two more recent studies compared different reduction strategies in a retrospective fashion. In PVAN diagnosed by using either protocol biopsy or decreased kidney function, Wadei et al<sup>49</sup> compared the strategy of transition from tacrolimus to CsA (goal CsA level, 125 to 175 ng/mL;  $n = 30$ ) to tacrolimus reduction (goal tacrolimus level, 4 to 6 ng/mL;  $n = 25$ ) in 55 patients who additionally underwent MMF reduction to 250 mg twice daily with or without cidofovir and intravenous immunoglobulin (IVIg). Neither IVIg nor cidofovir was independently associated with graft survival. Graft survival was equivalent in both groups, suggesting no benefit in transitioning from tacrolimus to CsA versus tacrolimus reduction. Weiss et al<sup>50</sup> recently compared an “aggressive” reduction strategy in which 1 drug (primarily the CNI) was

eliminated versus a more standard reduction of agents in a 3-drug regimen in PVAN associated with graft dysfunction (median serum creatinine at diagnosis, 2.5 mg/dL). Patients who underwent “aggressive” reduction had significantly better graft survival (1-year graft survival, 87.8% versus 56.2%;  $P = 0.03$ ). Notably, the majority of patients in the aggressive reduction arm remained on SRL/prednisone immunosuppression with goal SRL trough level less than 8 ng/mL, a strategy previously reported to be successful in a small case series of 3 patients.<sup>51</sup>

The development of acute rejection after dose reduction is a concern, and patients with traditional risk factors for rejection may be particularly susceptible.<sup>52</sup> After dose reduction, clearance of BK viremia is temporally associated with an increase in interferon  $\gamma$ -producing BK virus-specific lymphocytes,<sup>45,46</sup> suggesting reemergence of cellular immunity to BK virus. During this reestablishment of the immune response, alloresponsiveness also may become unmasked, with acute rejection rates as high as 10% to 15% reported.<sup>25,53</sup>

### Clinical Consideration No. 4: How Best to Manage Concurrent Acute Rejection and BKVAN?

In settings in which biopsy specimens show BKVAN and C4d staining in peritubular capillaries or mononuclear cell infiltrate in vessels, the diagnosis of concurrent acute rejection and BKVAN is straightforward and has been reported.<sup>54,55</sup> These diagnoses become more problematic when specific features of rejection are not present. More than half of all biopsy specimens with positive staining for polyomavirus will show tubulitis, which may or may not be caused by an alloimmune response (Fig 1). The decision to treat this histological finding as acute rejection in this scenario is a challenging one because it is clear that treatment with depleting antibody therapy or failure to reduce immunosuppression typically will result in further graft dysfunction.<sup>56</sup> Attempts to distinguish the infiltrating cells as allospecific or BK virus-specific with genomic,<sup>32</sup> proteomic,<sup>57</sup> and protein<sup>13,23</sup> expression have identified different “signatures,” but unfortunately have not been correlated with clinical outcomes. Treatment with corticosteroid boluses has been proposed,<sup>19</sup> but is of unproved benefit<sup>58</sup> and may do harm.<sup>59</sup> Our practice is to



**Figure 1.** Kidney transplant biopsy specimen from a 62-year-old man 5 months after receiving a deceased donor transplant and 4 months after receiving depleting antibody therapy for rejection. Serum creatinine level had increased from 1.1 to 1.4 mg/dL, with serum BK virus polymerase chain reaction of 62,000 copies/mL. (A) Periodic acid–Schiff stain shows areas of t3 tubulitis with greater than 10 mononuclear cells/tubular cross section, focal tubular basement membrane disruption (arrow), and i2 interstitial inflammation consisting of lymphocytes, plasma cells, and histiocytes affecting 30% of the total sampled renal parenchyma. No arteritis was identified in the sample. These findings met Banff 97 criteria for type IB acute cellular rejection. Viral cytopathic effect was not identified by using routine light microscopy. (B) Immunohistochemical staining for simian virus 40 large T antigen shows numerous positively staining nuclei in tubular epithelial cells (arrow) in areas of less severe interstitial and tubular inflammation, indicating active polyomavirus infection. Cytoplasmic staining is an artifact and does not represent infection. The patient underwent immunosuppression dose reduction alone with resolution of viremia 2 months later and serum creatinine level of 1.3 mg/dL. (Original magnification  $\times 400$ .)

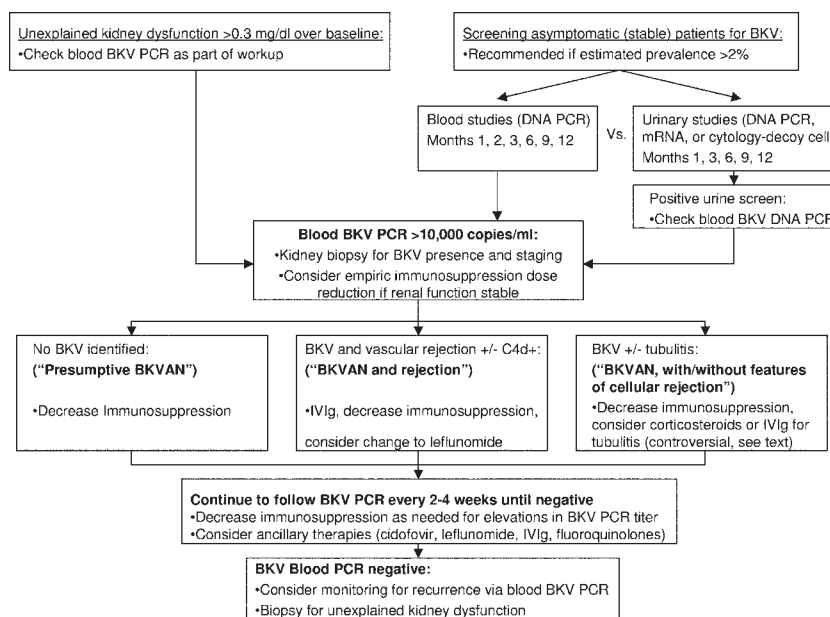
treat the findings of concurrent tubulitis and BKVAN with immunosuppression dose reduction without corticosteroid boluses, but consider the use of IVIg at low dose (100 mg/kg bi-weekly) during the first 8 weeks of immunosup-

pression reduction in the setting of continued deterioration in kidney function<sup>50</sup> (Fig 2).

#### **Clinical Consideration No. 5: Is There Added Benefit to Ancillary Therapies (IVIg, leflunomide, cidofovir, and fluoroquinolones)?**

After immunosuppression dose reduction, a slow decrease in PVAN activity typically occurs during weeks to months,<sup>60</sup> shown by using serial PCR sampling of blood. Despite this evidence of improvement, kidney function can temporarily deteriorate further, especially in the first month after diagnosis. Use of additional therapies often is considered during this phase in which minimal, if any, improvement is noted in kidney function. The ancillary therapies that have gained the greatest interest include the antiviral agent cidofovir, the antimetabolite leflunomide, such antibiotics as fluoroquinolones, and IVIg, an immunomodulatory agent (Table 4). Unfortunately, for all these additional therapies, no randomized prospective clinical trial has tested the value of adding these agents to the strategy of immunosuppression reduction alone.

Cidofovir is a viral DNA polymerase inhibitor that has antiviral activity against BK virus in vitro,<sup>61</sup> although BK virus does not encode viral DNA polymerases.<sup>62</sup> The mechanism for the inhibitory effect of cidofovir appears to be at the level of inhibition of intracellular BK virus genome replication, which is dependent on host cell replication factors, and thus this compound is associated with high degrees of host cell toxicity.<sup>63</sup> Clinically, cidofovir is a nephrotoxic agent associated with decreased kidney function and proteinuria at doses of 5 mg/kg/wk for treatment of cytomegalovirus disease. Cidofovir is highly concentrated in urine, and thus doses of 1/10 to 1/20 of cytomegalovirus treatment doses (eg, 0.25 to 0.5 mg/kg every 1 to 2 weeks) have been used in patients with BKVAN. In the largest cidofovir intervention trial to date,<sup>64</sup> 8 patients received cidofovir (0.5 to 1.0 mg/kg/wk for 4 to 10 weeks) and immunosuppression reduction versus 13 patients who underwent only immunosuppression reduction. Remarkably, 9 of the 13 lost graft function within 12 months versus 0 of 8 who received cidofovir. However, the investigators note that MMF may have been more systematically withdrawn in those who received cidofovir, emphasizing the need for a controlled trial.



**Figure 2.** BK virus management algorithm based on the current evidence. Given the paucity of prospective randomized trials, no single algorithm for BK virus can be classified as definitive. Abbreviations: BKV, BK virus; BKVAN, BK virus-associated nephropathy; PCR, polymerase chain reaction; IVIg, intravenous immunoglobulin; mRNA, messenger RNA.

Leflunomide is a pyrimidine analogue approved for the treatment of patients with rheumatoid arthritis. It also has anticytomegalovirus activity and appears to have activity against BK virus in vitro.<sup>61</sup> A case series of 26 patients with biopsy-proven BKVAN underwent CNI reduction, MMF discontinuation, and leflunomide addition (loading dose of 100 mg × 3, followed by 20- to 60-mg/d dose; leflunomide target trough

level, 50 to 100 ng/mL).<sup>65</sup> Fifteen percent graft loss occurred with stabilization of kidney function in the majority at more than 12 months of follow-up. However, others have not reported similar beneficial effects,<sup>66</sup> and a risk of hemolytic anemia at therapeutic goals has been reported.<sup>67</sup>

Fluoroquinolones have been proposed as a potentially efficacious therapy in patients with established BKVAN, based primarily on in vitro data suggesting activity against BK virus.<sup>68</sup> Clinical data for its effects in viral clearance are limited in the setting of kidney transplantation.<sup>69</sup>

Finally, IVIg has been used in patients with BKVAN as an immunomodulatory and potentially antiviral agent.<sup>70</sup> In 2 uncontrolled studies, IVIg was believed to be effective in preventing graft loss, but not clearance of viremia,<sup>71,72</sup> whereas in 2 comparative studies, the addition of IVIg to immunosuppression reduction was of no additional benefit.<sup>49,50</sup>

At this point, use of ancillary therapies should be viewed as an intervention that may have benefit, but also may carry harm given the side effects and nephrotoxicity<sup>73-75</sup> associated with these options.

**Table 4. Ancillary Therapies in BK Virus Nephropathy**

Intervention	Suggested Dose
Cidofovir	0.25-1.0 mg/kg IV biweekly for 8 wk without probenecid, prehydration recommended
Leflunomide	100 mg loading dose × 3 days, 20-60 mg/d, goal leflunomide trough 50-100 ng/mL (consider lower trough goals of 20-40 ng/mL given hemolysis risk, see text)
IVIg	1-2 g/kg IV × 1-2 doses or 150 mg/kg IV biweekly for 8 wk
Fluoroquinolones	Ciproflaxacin, 500 mg/d, duration dependent on virological response

Abbreviations: IV, intravenous; IVIg, intravenous immunoglobulin.

## SCREENING

Given the stepwise nature of BK virus presentation, from viremia to viremia to nephropathy and decreased kidney function, and the poor graft recovery rates when PVAN is diagnosed in the setting of decreased kidney function, screening for BK virus is indicated to identify and prevent the development of PVAN and permit earlier interventions. Two screening strategies have been proposed. An interdisciplinary recommendation suggests screening for viremia every 3 months during the first 2 years after transplantation and in the event of allograft dysfunction. If the urinary screen result is positive, a quantitative assay should be performed and followed with a biopsy if viral levels are sufficiently high.<sup>19</sup> Another proposed algorithm focuses on serum BK virus DNA PCR findings as the primary means of BK virus detection and prevention.<sup>76</sup> The primary reason for the discrepancy in these recommendations is the uncertainty of the value of urinary findings in clinical decision making because of the relatively high incidence of BK viremia without nephropathy (and thus low positive predictive value). Only after verification with quantitative tests is intervention recommended in both proposed strategies. The potential benefits of the first strategy include identification of not only BK, but also JC virus shedding through decoy cell identification in urine and identification of patients who may be at risk of future nephropathy earlier in the course of disease. The benefits of the second strategy are that it involves fewer tests, pinpoints clinical intervention to the results of 1 test, and may be more cost-effective. In the setting of graft dysfunction, it may be more prudent to initially screen through blood BK virus PCR given a greater positive predictive value and the potential to minimize the time to diagnosis (Fig 2). Screening should be considered for any patient with unexplained graft dysfunction because BKVAN can present very late after transplantation on stable doses of immunosuppression.<sup>77</sup> Both strategies have been used successfully in the prevention of BKVAN in both pediatric and adult populations.<sup>11,40,78,79</sup> Decisions regarding which strategy to use should take into account the local prevalence of PVAN and the availability and costs of testing. Importantly, a cost-effectiveness analysis confirms the

utility of PCR-based screening in transplantation populations that have a PVAN prevalence of more than 2.1%.<sup>80</sup>

## SCREENING NONRENAL SOLID-ORGAN TRANSPLANT RECIPIENTS FOR PVAN

Although the development of PVAN as a significant clinical entity has become overtly apparent during the last decade in kidney transplant recipients and has been identified in patients with other immune-compromised states,<sup>81</sup> its role in other immunosuppressed patient populations, such as heart, liver, and lung transplant recipients, is not clear. Only 7 cases of BKVAN in the native kidneys of nonrenal solid-organ transplant recipients have been reported in the literature (5 heart, 1 pancreas, and 1 lung).<sup>82-85</sup> Recently, a prospective study of BK viremia and viremia was performed in 60 recipients of heart, liver, and lung transplants in the first year after transplantation.<sup>86</sup> Fifteen percent of individuals (9 of 60 individuals, 16 of 193 samples) had detectable BK viremia, with a median viral load of  $1.12 \times 10^5$  copies/mL (range,  $1.1 \times 10^2$  to  $2.66 \times 10^8$  copies/mL). Importantly, no BK viremia was identified in any sample, and glomerular filtration rate was similar in those with versus without BK viremia at each time. Another longitudinal study of 50 stable lung transplant recipients (mean time from transplantation,  $3.7 \pm 2.9$  years) found a 24% incidence of BK viremia, again with no association between viremia and decreased kidney function.<sup>87</sup> Finally, a cross-sectional study of BK viremia in 35 nonrenal solid-organ transplant recipients reported a 15% incidence of viremia, but no viremia or correlation with decreased kidney function.<sup>88</sup> These studies suggest that BK reactivation is common in solid-organ transplant recipients, but additional factors may be necessary to lead to kidney injury,<sup>89</sup> perhaps immunity related<sup>47</sup> or factors related to the surgical procedure itself.<sup>90</sup> Interestingly, BK virus reactivation is very common in bone marrow transplant recipients, in whom the most common clinical manifestation is not decreased kidney function, but hemorrhagic cystitis.<sup>10,91</sup> This emphasizes that a factor or factors unique to kidney transplantation are important to initiate a cascade of events that lead to interstitial nephritis.



## RETRANSPLANTATION AFTER GRAFT LOSS

An increasingly common clinical consideration is the safety and timing of retransplantation in patients who have experienced graft loss from BKVAN because many factors that led to graft loss (eg, recipient immunity, the presence of BK viremia) may persist at the time of consideration for retransplantation. Fortunately, successful retransplantation after BK virus–related graft loss seems to be the rule<sup>33,92-95</sup> rather than the exception,<sup>96</sup> with a combined incidence of recurrent BKVAN in these studies of 15%.<sup>97</sup> Although nephrectomy of the failed allograft does not seem to be required before retransplantation, most cases of successful retransplantation had undergone prior allograft nephrectomy, and all successful cases had a documented absence of viral replication.

### Clinical Consideration No. 5: Can Preemptive Transplantation Be Considered for Patients With Failing (But Still Functional) Allografts Because of BKVAN?

There has been general reluctance to pursue preemptive retransplantation while BK virus activity is still evident, based on a single case report of recurrent BKVAN and graft failure in a patient with prior BKVAN.<sup>96</sup> However, there was 1 report of 2 patients with active viremia and failing allografts who underwent successful retransplantation with abrupt clearance of viremia.<sup>98</sup> In these cases, immunosuppression had been reduced and BK virus titers were decreasing at the time of retransplantation, suggesting that antiviral immunity was reemerging, and nephrectomy was performed concurrent with retransplantation, shown previously to effectively clear viremia.<sup>99</sup> Until greater experience is reported, it is prudent to document the lack of viral activity by using blood PCR measures before preemptive transplantation. Whether BK viremia must also be absent or nephrectomy of the failing allograft must be performed is unclear.

## SUMMARY

During the last decade, many advances in understanding the biological characteristics of PVAN and clinical management of kidney transplant recipients with PVAN have been made. Goals for the near future include additional re-

search to clarify risk factors for the development of disease and evaluation of cost-effective screening strategies to help prevent PVAN. Prospective randomized trials should be performed to assess the value of ancillary therapies versus immunosuppression reduction alone in patients with established PVAN. As these goals are accomplished, PVAN may recede as the leading infectious disease that contributes to kidney allograft loss.

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