BK virus infection: an update on diagnosis and treatment

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ABSTRACT

BK virus, first isolated in 1971, is a significant risk factor for renal transplant dysfunction and allograft loss. Unfortunately, treatment options for BK virus infection are limited, and there is no effective prophylaxis. Although overimmunosuppression remains the primary risk factor for BK infection after transplantation, male gender, older recipient age, prior rejection episodes, degree of human leukocyte antigen mismatching, prolonged cold ischemia time, BK serostatus and ureteral stent placement have all been implicated as risk factors. Routine screening for BK has been shown to be effective in preventing allograft loss in patients with BK viruria or viremia. Reduction of immunosuppression remains the mainstay of BK nephropathy treatment and is the best studied intervention. Laboratory-based methods such as ELISPOT assays have provided new insights into the immune response to BK and may help guide therapy in the future. In this review, we will discuss the epidemiology of BK virus infection, screening strategies, treatment options and future research directions.

Keywords: BK virus, diagnosis, kidney, transplantation, treatment

INTRODUCTION

With the introduction of more potent immunosuppression regimens and decreased acute rejection rates, viral infections after renal transplantation have emerged as an important cause of allograft loss. BK is a common posttransplant opportunistic viral infection, affecting ~15% of renal transplant recipients in the first posttransplant year and lacking an effective prophylaxis strategy. Treatment options are limited and if unaddressed, BK nephropathy (BKVN) will progress to allograft failure. In this review, we will address the utility of BK screening, methods of detection, new diagnostic tools and current management options.
tion can present either as BKVN or hemorrhagic cystitis. There have been scattered case series reporting detectable BKV and BK viruria in nonrenal solid organ transplant recipients [16–19] (heart, lung and liver), but in general the presence of BK in blood or urine has not been associated with impaired renal function in these patients.

**RISK FACTORS**

The most consistent risk factor identified across studies for the development of BKVN is the overall degree of immunosuppression [20]. Other hypothesized risk factors for BKV and BKVN include male gender, older recipient age, rejection episodes, degree of human leukocyte antigen (HLA) mismatching, prolonged cold ischemia, BK serostatus and ureteral stent placement [20, 21], but these have not been uniformly observed in all studies (Table 2).

Induction and also maintenance immunosuppression appears to influence BKVN risk. An analysis of the Organ Procurement and Transplantation Network (OPTN) data from the USA by Dharnidharka et al. [25] surveyed the outcomes of over 48,000 kidney transplants performed between 2003 and 2006; they demonstrated that the use of rabbit anti-thymocyte globulin induction and tacrolimus- or mycophenolate mofetil (MMF)-based immunosuppression increased the risk for the development of BKV. Interestingly, induction with alemtuzumab was not a significant risk factor in a large registry study [25], congruent with other single-center retrospective cohort studies which also failed to show an increased incidence of BKV in patients administered alemtuzumab [26–28]. The observation that maintenance immunosuppression impacts BKVN risk is bolstered by a secondary analysis of data from the DIRECT trial. The DIRECT trial was a prospective, randomized trial of cyclosporine versus tacrolimus in conjunction with basiliximab induction, designed to study the development of new-onset diabetes mellitus or impaired fasting glucose in renal transplant recipients. Hirsch et al. [14] performed a secondary analysis of the data and demonstrated that patients in the cyclosporine arm had a lower rate of BKV at 6 and 12 months posttransplant, compared with the tacrolimus group. High-titer BKV (>4 log) and the overall median BK viral loads were higher in the tacrolimus group. This study is suggestive of an effect of maintenance immunosuppression on BK reactivation, but as it is a secondary data analysis should be interpreted with caution; furthermore, patients in the tacrolimus group were maintained at high trough levels (10–15 ng/mL) during Months 1–3 and 5–10 ng/mL during Months 4–6 and exposed to higher doses of steroids early on after transplant, which may have affected their risk of developing BKV. The analysis of national registry data [25] has also suggested an effect of maintenance steroids on the development of BKV, although the hazard ratio associated with steroid use was modest (HR 1.16, 95% CI 1.02–1.31). Prospective studies designed to address the effect of induction and maintenance immunosuppression on BKVN are warranted.

Donor and recipient characteristics may also play a role in the development of BKV and BKVN. An association has been described between specific HLA alleles and the risk for BK; a single-center report [22] noted that the absence of the HLA C7 allele in the donor or recipient increased the risk for sustained BKV in the recipient at least 3-fold. Recipient race may also affect a patient’s risk of developing BKV; in a prospective study designed to identify risk factors for BK infection, Sood et al. [13] demonstrated that a lower proportion of African Americans developed BKV, independent of other confounding risk factors. Nonimmunosuppression-based interventions, such as ureteral stent placement, can also confer the risk of developing BK. At least three single-center reports [9, 23, 24] have described an increased risk of BKV in patients who had a ureteral stent (OR 3.0–5.6), suggesting that perhaps these patients should be screened earlier or more often.

Currently, unlike testing for cytomegalovirus, pretransplant screening of donors and recipients for BK seropositivity is neither mandatory nor routinely performed. Pretransplant BK antibodies are not clearly protective; pretransplant BK seropositivity in adult recipients has not been shown to influence the development of BKVN after transplantation [8, 29]. However, there is growing evidence to suggest that the donor kidney may be the source of posttransplant BKV and BKVN [22], and that pretransplant screening of donors could identify recipients at greatest risk of developing BK. Bohl et al. [22] identified BK virus antibody-positive donors as a risk factor for posttransplant BKV in recipients; in their study, patients who received a kidney from a BK-seropositive donor were more likely to develop BK infection (46%), compared with those whose kidney came from a seronegative donor (15%). Overall, they found a higher than expected concordance between donor and recipient BK serostatus. Interestingly, all of the pairs in which both donor and recipients were BK antibody-positive shared the same viral subtype and sequence, suggesting donor origin of the BK virus. Recipients of BK

<table>
<thead>
<tr>
<th>Reference</th>
<th>Decoy cells (%)</th>
<th>BK viruria (%)</th>
<th>BKV (%)</th>
<th>BKVN (%)</th>
<th>Graft loss due to BK (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hirsch et al. [8]</td>
<td>29</td>
<td></td>
<td>13</td>
<td>6.4</td>
<td>0</td>
</tr>
<tr>
<td>Brennan et al. [9]</td>
<td></td>
<td></td>
<td>11.5</td>
<td>*</td>
<td>0</td>
</tr>
<tr>
<td>Koukoulaki et al. [10]</td>
<td></td>
<td></td>
<td>14</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Almeras et al. [11]</td>
<td></td>
<td></td>
<td>11</td>
<td>0.85</td>
<td>0.85</td>
</tr>
<tr>
<td>Thakur et al. [12]</td>
<td>15.7</td>
<td></td>
<td>43</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Sood et al. [13]</td>
<td>17</td>
<td></td>
<td>27</td>
<td>2.1</td>
<td>0</td>
</tr>
<tr>
<td>Hirsch et al. [14]</td>
<td>25.4</td>
<td></td>
<td>13.7</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

*a* Prevalence of event not reported.
seropositive donor kidneys developed BKV at earlier posttransplant timepoints, had higher viral titers and were slower to clear the virus. These data suggest a role for donor pretransplant serotyping as a means of BK risk assessment and immunosuppression management.

**SCREENING**

As BKVN has limited treatment options, the goal of screening is to facilitate early diagnosis of patients when viruric or viremic, and to intervene prior to the development of overt nephropathy. Prospective screening studies have demonstrated that BKVN is predominantly an early complication of renal transplantation with most cases occurring within the first posttransplant year. In a cohort of Greek renal transplant recipients followed prospectively for 18 months after transplant [10], the incidence of viremia and viruria peaked at Month 3 with 28 and 31%, respectively, of patients testing positive. Incidence of BK peaked a second time at 12 months posttransplant, but fewer cases overall were diagnosed, and only one case was reported with first detection of BK at 18 months posttransplant. The French experience is similar; Almeras et al. [11] followed 119 patients for 12 months; in that time period, 10.9% of patients had detectable BKV and the median time to a detectable viral load was 90 (23–214) days. All viremic patients had allograft biopsies and only one was diagnosed with BKVN; all patients had an initial viral load <4 log copies per mL (range 2.69–3.45 log). Similar findings were noted by Thakur et al. [12]; of the 32 patients they followed prospective ly with BK viral loads and protocol biopsies, the highest incidence of positive BK viral loads was noted at 1 month posttransplant and none of the protocol biopsies demonstrated histology consistent with BKVN. Based on these reports and others, we routinely screen all renal transplant patients at our center for BK starting at 3 months posttransplant and have found that new onset BK after 24 months posttransplant is rare [30]; we do not recommend screening beyond 24 months unless renal dysfunction is present. However, as per the recently published AST Infectious Disease Community of Practice guidelines [21] and older KDIGO guidelines [31], earlier (starting at 1 month posttransplant) and more frequent screening (monthly plasma screening for the first 6 months, then every 3 months until 2 years posttransplant) may be more appropriate in high incidence transplant centers. Our center and others [32, 33] have found prospective screening for BKV with subsequent immunosuppression reduction to be an effective means of preventing allograft loss due to BKVN. Reported acute rejection rates after a decrease in immunosuppression ranged from 8 to 12% and most were responsive to steroid treatment [33, 34]. We recommend that patients who have their immunosuppression reduced for BKV should be monitored carefully with a serum creatinine checked every 1–2 weeks and BK viral loads repeated at 2–4 week intervals.

**SCREENING TESTS**

BK virus is detectable in both blood and urine. After BK reactivation, the virus is first detectable in the urine, with viremia developing several weeks later. There have been isolated case reports of patients developing viremia without viruria, but this is unusual. BKV has a higher positive predictive value (PPV) for BKVN (50–60%) than BK viruria [34]; hence screening for BKV is the preferred screening strategy at many institutions. Table 3 summarizes the screening methods commonly used.

BK viral loads are measured by real-time PCR; a BK-specific sequence is amplified with a fluoroscent probe and the number of amplicons produced is compared with a standard curve generated with serial dilutions of a known concentration of BK DNA. There is no established standard assay, and intra-laboratory variations in the assay standards or protocols used can yield significant differences in the amount virus quantified and limits of assay detection. Variations in sample type/source, DNA extraction techniques, primer and probe sequences, and BK strain DNA used for standard curve creation can all impact assay results and introduce clinically significant variability [34, 38]. Most quantitative PCR assays use the genotype I (Dunlop) strain as the reference sequence against which primers and probes are designed [39]. In a comparison of the PCR results generated from seven different commercially available kits using the Dunlop strain or the mixed patient standard (MPS) as the reference sequence, discordant results (>1 log difference) were found in 23% of assays using the MPS and 94% of assays using Dunlop as the standard [40]. This effect was most pronounced in the subtype III and IV isolates [40], and was attributed to primer/probe mismatch as well as DNA sequence

### Table 2. Summary of proposed risk factors for BK virus infection

<table>
<thead>
<tr>
<th>Donor risk factors</th>
<th>Degree of HLA mismatching</th>
<th>HLA C7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient risk factors</td>
<td>Older recipient age</td>
<td>Male recipient</td>
</tr>
<tr>
<td>Transplant risk factors</td>
<td>Acute rejection episodes</td>
<td>Cold ischemia time</td>
</tr>
</tbody>
</table>

| Table 3. Summary of BKV screening methods

<table>
<thead>
<tr>
<th>Screening method</th>
<th>Positive predictive value (%)</th>
<th>Negative predictive value (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decoy cells [8]</td>
<td>29</td>
<td>100</td>
<td>25</td>
<td>84</td>
</tr>
<tr>
<td>Hauen [35]</td>
<td>97</td>
<td>100</td>
<td>100</td>
<td>99</td>
</tr>
<tr>
<td>BK urine PCR [8, 36, 37]</td>
<td>40</td>
<td>100</td>
<td>100</td>
<td>78</td>
</tr>
<tr>
<td>BK serum PCR [8, 36, 37]</td>
<td>50–60</td>
<td>100</td>
<td>100</td>
<td>88</td>
</tr>
</tbody>
</table>
polymorphisms. Another group [39] confirmed that BK PCR assays using the genotype I strain as the reference can be as much as 4-fold less sensitive for variant strains (limit of detection 10,000 copies per μL for the variant strain compared with 10 copies per μL for genotype I). This is problematic as rare BK virus subtype variants are more frequently associated with BKVN [4], perhaps due to the difficulty in detecting them at low viral loads. To limit intralaboratory fluctuations in BK PCR results, we recommend using a consistent laboratory facility to monitor a single patient whenever feasible and to have a low clinical suspicion for rare variants when a patient’s clinical course does not correlate with his viral load.

**Blood**

BK detection by real-time PCR of plasma is very sensitive and specific for the development of BKVN. Depending on the study, sensitivity can approach 100% and specificity is ∼90%, with a PPV of 50% and negative predictive value (NPV) of 100% [8, 41]. This is the preferred screening method at most transplant centers, including our own. A definitive viral load cutoff associated with nephropathy has not been established, but retrospective studies have suggested that a BK viral load >4 log copies/mL is strongly associated with finding BKVN on biopsy [42].

**Urine**

BKV shedding in the urine is common and can occur in up to 30% of renal transplant recipients [20]. Urine can be screened for BK by cytology or by quantification of urine BK DNA by PCR. Tubular epithelial cells infected with BK virus are shed in the urine and are called ‘decoy cells’ (Figure 1). They have large, basophilic nuclei with viral inclusions and appear similar to those seen in uroepithelial cancer. Urine BK PCR is more sensitive than urine cytology for detection and diagnosis of BKVN. In a comparison of urine cytology with urine PCR, decoy cells had a sensitivity of only 25% and a specificity of 84% for BKVN compared with urine PCR which was 100% sensitive and 78% specific [41]. This is in contrast to an earlier study in which urine decoy cells were found to be 100% sensitive and 71% specific for BKVN with a positive predictive value (PPV) of 29% and NPV of 100% [8]. If only urine BK screening is to be performed, we recommend urine BK PCR as the superior assay, using the threshold of >1 × 10^7 copies/mL as suggestive of BKVN. Given the widespread availability of the plasma PCR assay and its greater predictive value for BKVN, it is unnecessary to perform urine BK screening first before plasma testing.

**EM Haufen**

Haufen are icosahedral aggregates of polyomavirus particles and Tamm-Horsfall protein that can be detected in the urine of kidney transplant patients with BKVN using negative-staining electron microscopy. In a single-center study [35] of 21 kidney transplant recipients with biopsy-proven BKVN, the presence of Haufen in the urine was highly correlated (k 0.98) with BKVN and had a PPV of 97% for BKVN. These results are intriguing and require further study, but if validated could offer a noninvasive alternative for diagnosing BKVN.

**Urine mRNA**

There is growing interest in the use of mRNA profiles in nephrology as a biomarker for native renal disease, acute rejection and chronic allograft dysfunction. BK viral capsid protein 1 (VP1) mRNA derived from urinary cells has been studied as a BKVN biomarker [35]. In a previous publication [43], a cutoff value of 6.5 × 10^5 VP1 mRNA/ng RNA was established as a threshold that was predictive of BKVN. This threshold was validated in a second cohort of patients [44], 12 of whom had biopsy-proven BKVN. Urine granzyme B mRNA and pro tease inhibitor-9 mRNA levels were also shown to be predictive of subsequent decline in allograft function, suggesting new areas of future investigation. Urine mRNA profiles may provide additional diagnostic and prognostic information in addition to renal transplant biopsy.

**Renal biopsy**

Renal biopsy remains the gold standard for the diagnosis of BKVN. It is recommended in patients with a high level of BKV (>4 log copies/mL), with or without an elevation in serum creatinine. The histology of BKVN is characterized by tubular atrophy and fibrosis with an inflammatory lymphocytic infiltrate that can be mistaken for acute cellular rejection. The presence of intranuclear BK virus inclusion bodies which stain positive for the large T antigen is pathognomonic for BKVN. Biopsy findings can be focal in nature, and along with the possibility of sampling error, making diagnosis on occasion challenging. Owing to these challenges, a negative biopsy cannot rule out early BKVN with 100% certainty. A minimum of two cores including some medulla is recommended to make a correct diagnosis. The prognostic potential of biopsy findings has been studied; the degree of fibrosis and tubular atrophy appears to be the most predictive of allograft outcome [45]. At least three different histologic grading systems exist to classify the degree of BK-related injury seen on renal transplant biopsy (Table 4). The series from the Mayo Clinic [48] was the first to identify the utility of quantifying the number of infected tubular cross-sections and incorporating that data into the standard Banff criteria for chronic allograft injury, which

![FIGURE 1: Decoy cells in the urine.](https://academic.oup.com/ndt/article-abstract/30/2/209/2337134 by guest on 23 March 2019)
assesses interstitial fibrosis, tubular atrophy, arterial fibrous intimal thickening and hyaline arteriolar sclerosis. More recently, Drachenberg et al. [46] at the University of Maryland have proposed an alternate schema, which focuses predominantly on the degree of fibrosis and inflammation. Masutani et al. [45] demonstrated that inflammation and fibrosis are important prognostic parameters in determining the outcome of BKVN, whereas BKV induced tubular injury and histologic viral load are not informative, suggesting a modification to the Banff Working Proposal to incorporate the degree of inflammation into the morphologic criteria used for staging this disease.

No single grading system has emerged as predominant. To date, only the Banff grading system has been tested for intraobserver variability [47]; the Banff working proposal has been shown to have moderately good intraobserver agreement, with a kappa score of 0.47 (0.35–0.60, P < 0.001) [47]. The establishment and validation of a uniform grading system will be important for clinical care in order to assess prognosis and for clinical trials of BK treatment to judge response to therapy.

**CELLULAR IMMUNE RESPONSE TO BK**

Cellular adaptive immunity is essential for the control of BKV and resolution of BKVN. CD4+ and CD8+ T cells both have a role in BK clearance. T-cell responses are directed against both nonstructural and BK capsid proteins and can be measured via ELISPOT and tetramer staining. Monitoring for the development of anti-BK T cells and their functionality may provide additional prognostic information regarding a timeline for recovery.

Anti-BK T cells can be found in both healthy volunteers and kidney transplant recipients. Using tetramers and T cells from HLA-A*0201 individuals, Chen et al. [49] were able to determine whether CD8s from healthy volunteers responded to different VP1 viral epitopes than CD8 T cells from patients with BKVN. In transplant recipients, a strong CD8 response was associated with lower BK viral loads in blood and urine, whereas weak responses correlated with high BK titers and viral persistence [49, 50]. Similar CD8 responses have been elicited with the large T antigen [51]. Interferon-γ ELISPOT assays have demonstrated that CD4 responses are targeted towards the large T antigen, VP1 capsid protein [52] and VP3 [53].

In further studies [54], the development of BK-specific cellular immune responses as measured by (interferon) IFN-γ ELISPOT correlated with resolution of BKVN. Schachtner et al. [55] compared ELISPOT results from three groups of patients—those with BKVN, those with transient viremia and those who were BK seropositive but never viremic. All patients with BKVN or transient BKV had low or undetectable T-cell responses at the time of BK reactivation. Patients who cleared the virus (limited viremia) developed anti-BK T-cell responses within 1 month after diagnosis and the development of anti-BK T-cells coincided with BKV clearance. Patients with biopsy-proven BKVN required significantly longer time (median time 5 months) to develop anti-BK cellular
immunity. T-cell responses to structural proteins VP1, VP2 and VP3 were detected earlier than those against the small t and large T antigens.

Cytokine production by BK-specific T cells is also informative. Trydzenskaya et al. [56] measured the percentage of polyfunctional, BK-specific IFN-γ/interleukin-2/tumor necrosis factor-α producing CD4 T cells in three groups of patients: those with prolonged high-titer BK reactivation, those with viral clearance in <3 months and those with BK seropositivity but no reactivation. In their analysis, they found that patients with rapid clearance and those who were seropositive only had higher frequencies of polyfunctional, anti-BK CD4 T cells. Assays to assess BK-directed cellular immunity and anti-BK T-cell phenotype may provide additional prognostic information regarding viral clearance and patient recovery, and are an active area of investigation.

**TREATMENT**

Reduction of immunosuppression is the mainstay of BKVN treatment. Management approaches differ and can include discontinuation of the anti-metabolite, dose reduction of the calcineurin inhibitor (CNI) by 25–50% targeting significantly lower levels (tacrolimus 3–4 ng/mL and cyclosporine 50–100 ng/mL, or even less) or switching from tacrolimus to cyclosporine (Table 5). Discontinuation of the anti-metabolite such as MMF is the most common approach, but a recent study [63] suggests that both tacrolimus and cyclosporine can inhibit anti-BK T-cell responses in vitro, challenging this practice. Other treatment alternatives can include use of leflunomide, cidofovir, ciprofloxacin, rapamycin or intravenous immunoglobulin (Table 5). Objective data regarding BK treatment are limited; a meta-analysis [64] of all published approaches to BK treatment found only 3 randomized controlled trials, 9 cohort studies and 29 case series. Regardless of the treatment strategy employed, rapid viral reduction has been associated with stable or improving glomerular filtration rate (GFR) [65].

Screening with subsequent immunosuppression reduction was shown to be effective in preventing allograft loss in single-center studies. Schaub et al. [33] followed 194 renal transplant recipients for 5 years posttransplant; patients with detectable BKV had their CNI dose decreased in a stepwise fashion. BKV resolved in 92% of patients and no difference was observed in 1- and 3-year allograft survival between the BK-viremia group and the no BK group. Another single-center report [13] in which both the CNI and MMF were reduced simultaneously showed similar results; BKV declined in most patients while estimated GFR (eGFR) remained stable and no allografts were lost in the BKV group. A longer term follow-up is equally encouraging. Hardinger et al. [59] demonstrated at 5-year follow-up of their cohort of 194 patients a similar efficacy and safety for immunosuppression reduction as in the shorter term studies. In their study, patients with BKV or BKVN treated with immunosuppression reduction had no difference in patient or allograft survival compared with those without. Patients maintained on tacrolimus-containing regimens were shown to have lower acute rejection rates and higher eGFRs despite BK.

In their meta-analysis, Johnston et al. [64] did not find an allograft survival benefit with the addition of cidofovir or leflunomide to immunosuppression reduction, and clinical studies

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Reference</th>
<th>Immunosuppression adjustment strategy</th>
<th>Patients with BKV or BKVN</th>
<th>Outcome</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunosuppression reduction</td>
<td>Hirsch et al. [8]</td>
<td>Varied; CNI minimization or switch of agent</td>
<td>5</td>
<td>4/5 cleared BKV</td>
<td>-Three episodes of rejection</td>
</tr>
<tr>
<td></td>
<td>Almeras et al. [57]</td>
<td>CNI and MMF dose reduction simultaneously</td>
<td>11</td>
<td>8/11 cleared BKV</td>
<td>-No allograft losses to BKVN</td>
</tr>
<tr>
<td></td>
<td>Weiss et al. [58]</td>
<td>Withdrawal of CNI or MMF versus dose reduction of both CNI and MMF</td>
<td>35</td>
<td>19/35 retain allograft function</td>
<td>-Three episodes of rejection</td>
</tr>
<tr>
<td></td>
<td>Schaub et al. [33]</td>
<td>CNI minimization followed by discontinuation of MMF</td>
<td>38</td>
<td>35/38 cleared BKV</td>
<td>-CNI withdrawal is associated with superior allograft survival compared with dose reduction strategy</td>
</tr>
<tr>
<td></td>
<td>Hardinger et al. [59]</td>
<td>MMF discontinuation followed by minimization of the CNI</td>
<td>23</td>
<td>12/23 cleared BKV</td>
<td>-Three episodes of acute rejection</td>
</tr>
<tr>
<td></td>
<td>Faguer et al. [60]</td>
<td>MMF replaced with leflunomide</td>
<td>11</td>
<td>5/11 cleared BKV</td>
<td>-No graft losses due to BK</td>
</tr>
<tr>
<td></td>
<td>Leca et al. [61]</td>
<td>MMF replaced with ‘low-dose’ or ‘high-dose’ leflunomide</td>
<td>21</td>
<td>11/21 cleared BKV</td>
<td>-No difference in patient or kidney survival with BK</td>
</tr>
<tr>
<td></td>
<td>Kuypers et al. [62]</td>
<td>MMF/CNI reduction with/without ‘adjuvant’ cidofovir</td>
<td>21</td>
<td>6/8 cidofovir patients cleared BKV</td>
<td>-Five episodes of acute rejection</td>
</tr>
</tbody>
</table>

Table 5. Summary of treatment strategies for BKV and BKVN
are at best inconclusive. One single-center trial [62] of 21 patients compared immunosuppression reduction alone versus addition of cidofovir and found better allograft survival with cidofovir use but no difference in BK clearance. Many other studies [66, 67] have failed to find a benefit with cidofovir use, and the risk of renal side effects is significant. In a single-center case series [68], leflunomide was reported to be an effective treatment for BKVN and only 5% of patients treated lost their allografts; however, most studies have not demonstrated a benefit with the addition of this agent. At this time, we do not recommend the use of cidofovir or leflunomide as adjuvant therapy for BKVN.

A phase II trial [69] has looked at the efficacy of FK778 for the treatment of BKVN. FK778 is a derivative of the active metabolite of leflunomide and inhibits pyrimidine biosynthesis to prevent lymphocyte proliferation. FK778 did decrease BKV and BK viruria in patients treated with it, but acute rejection rates and incidence of allograft loss in the FK778 treatment group were much higher than in the immunosuppression reduction group [69]. No further studies using FK778 are planned at this time.

**UPDATE: CLINICAL TRIALS**

There are currently four BK infection treatment trials open on the NIH clinical trials website (www.clinicaltrials.gov) [70]; three are actively recruiting patients (NCT01789203, NCT01649609 and NCT01620268) and the fourth is enrolling by invitation only at this time (NCT01624948). NCT01789203 is a randomized, placebo controlled trial of ciprofloxacin for the prevention of BKV or BKVN. NCT01649609 is a randomized trial comparing the efficacy of reduction of immunosuppression versus substitution of tacrolimus for sirolimus for the treatment of BKV or BKVN. NCT01620268 is an open-label trial using a combination of leflunomide and orotic acid in patients with high levels of BK viruria. In the fourth trial, NCT01624948, patients with BKV will be randomized to either 50% mycophenolate dose reduction or substitution of MMF with everolimus. These trials will hopefully provide new therapeutic options for patients with BKV and BKVN.

**RETRANSPLANTATION**

Retransplantation after allograft loss due to BKVN is a reasonable option. A recent review of the OPTN database [71] for transplants performed from June 2004 to December 2008 revealed that 823 allografts were lost to BKVN during this time period. Of the 126 retransplants, only one kidney was lost due to recurrent BKVN. One- and 3-year allograft survival in the retransplanted patients was excellent at 98.5 and 93.6%, respectively [71]. Although kidney transplant loss due to BKVN should not be a barrier to retransplantation, pretransplant clearance of BK viral load is necessary. Transplant nephrectomy in patients with failed graft due to BKVN has not been found protective after retransplantation.

**CONCLUSION**

BK infection is a relatively common and early posttransplant complication after kidney transplantation. Careful screening can prevent allograft loss and should be employed. Serum BK PCR is the preferred screening method but alternatives exist. Translational laboratory-based assays are being developed that may provide additional information regarding patient clinical course in the future. The mainstay of treatment remains careful reduction of immunosuppression and close monitoring for the development of acute rejection. Prospective studies a with longer follow-up are still needed to evaluate different treatment strategies while assessing the possibility of chronic allograft dysfunction due to systematic reduction of immunosuppression.

**CONFLICT OF INTEREST STATEMENT**

The authors have no financial conflicts of interest to disclose.

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ABSTRACT

In this position article, DESCARTES (Developing Education Science and Care for Renal Transplantation in European States) board members describe the current strategies aimed at expanding living and deceased donor kidney pools. The article focuses on the recent progress in desensitization and kidney paired exchange programmes and on the expanded criteria for the use of donor kidneys and organs from donors after circulatory death. It also highlights differences in policies and practices across different regions with special regard to European Union countries. Living donor kidney paired exchange, the deceased donor Acceptable Mismatch Programme and kidneys from donors after circulatory death are probably the most promising innovations for expanding kidney transplantation in Europe over the coming decade. To maximize success, an effort is needed to standardize transplant strategies, policies and legislation across European countries.

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