BK Polyomavirus in Renal Transplantation

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Abstract

BK virus is a human polyomavirus that rarely causes disease, except in immune-compromised patients. Evidence of prior BK Virus (BKV) infection is highly prevalent in the general population, and although it rarely causes significant morbidity at primary infection, reactivation of BKV after kidney transplantation is recognized as a cause of BKV-associated Nephropathy (BKVAN), ureteric stenosis, and, rarely, haemorrhagic cystitis. The incidence of BKVAN appears to be increasing, most likely because of increased surveillance post-transplant, as well as the use of more potent immunosuppressive agents. Many patients with BKVAN experience progressive kidney dysfunction and the disease represents a significant threat to long-term kidney transplant success. This narrative review will discuss the epidemiology, risk factors, clinical features, screening, diagnosis and management of BKV infection in the setting of kidney transplantation, as well as suggest future research directions.

Keywords: BK polyomavirus; Renal transplantation; Immunocompromised, BKVAN

Introduction

BK Virus (BKV) is a circular, double-stranded DNA virus from the polyomavirus family (Table 1). It was first discovered in the urine of a kidney transplant recipient who had the initials BK2 and is now known to be ubiquitous in humans. Primary infection with BKV appears to be subclinical and typically occurs during childhood. The sero-prevalence is high, measured at 82% in a population of healthy Swiss adult blood donors and 98% in healthy 7-9-year-old Finnish children [1-3]. Following primary infection, BKV establishes permanent latency within the uro-epithelium and renal tubular epithelial cells [4]. Asymptomatic urinary BKV shedding was detectable in 8% of healthy BKV seropositive immune-competent individuals. BKV rarely causes disease unless patients are immune-compromised, such as occurs in the setting of immunosuppression for kidney transplantation. Outside of renal transplantation, BKV is also encountered within bone marrow transplant recipients and in patients with HIV where it also presents as BKV associated nephropathy and haemorrhagic cystitis [4,5]. This narrative review will specifically focus on the epidemiology, risk factors, clinical features, screening, diagnosis and management of BKV infection in the setting of kidney transplantation, as well as suggest future research directions.

| Virus       | Clinical phenotype                               |
|-------------|--------------------------------------------------|
| BK          | BK-virus Associated Nephropathy (BKVAN), ureteric stenosis, haemorrhagic cystitis in immune-compromised patients |
| JC          | Progressive multifocal leuko-encephalopathy in immune-compromised patients |
| KI          | Respiratory tract infection                      |
| WU          | Respiratory tract infection                      |
| Merkel cell virus | Neuroendocrine skin cancer (Merkel cell cancer) |

Table 1: Polyomaviridae that infect humans.

Epidemiology: BK Viruria develops in 30% of transplant recipients and progresses to viremia and BK associated nephropathy in 13% and 7-8% of transplant recipients, respectively [4,6-8]. This progressively affects graft function and increases the risk of graft loss from <10% to approximately 40% at 3 years follow up [9,10]. Even higher rates of graft loss have been described among patients with reactory BK BKVAN or concurrent acute rejection [11,12]. Registry data indicate that BK viraemia and BKVAN incidence continues to rise with more recent transplant year and the widespread use of potent immunosuppressive drug regimens [13,14]. The substantial decrease in acute rejection rates observed in most centers has not resulted in improved rates of late allograft failure [15], and BKVAN has an important impact on long-term graft function and survival [16-18].
BKV infection may cause ulceration and stenosis of the transplant ureter usually at the site of ureteric anastomosis. BKV-associated ureteric obstruction has been reported in 3% of renal transplant patients, occurring between 50 and 300 days post-transplant [19], and has rarely been described following haematopoietic stem cell transplant [20]. Haemorrhagic cystitis due to BKV is a common occurrence (about 10%) following haematopoietic stem cell transplantation [21,22]. The incidence following renal transplantation is unknown.

**Risk Factors:** The most consistent risk factor identified across studies is the overall degree of immunosuppression [23] (Table 2). Induction therapy with anti-thymocyte globulin (ATG) is consistently associated with sustained viraemia and BKVAN when compared with induction with basiliximab [13,24,25] or no induction7. Use of ATG for either induction or management of acute rejection is associated with a higher incidence of BKVAN on multivariate analysis (3.53% versus 1.44%; P=0.048) [26]. Basiliximab (anti-CD25 mAb) has not been shown to influence BK infection rates [13,27]. The influence of the induction agent, alemtuzumab, is at this stage unclear. Some groups report no increase in rates of BKV in patients following induction therapy with alemtuzumab (anti-CD52 mAb) compared with induction with less potent agents [28]. The recent Oxford 3C trial reported significantly higher rates of BK viraemia or BKVAN at six-months after induction with alemtuzumab compared to basiliximab (8% vs. 4%, hazard ratio 1.92 (95% CI 1.06-3.45) p=0.03) [29]. Desensitisation of highly HLA-sensitised patients with IVIG and Rituximab is also associated with a significantly higher incidence of BK Viraemia [30].

| Risk Factor                                      | Reference          |
|-------------------------------------------------|--------------------|
| Immunosuppressive Regimen                       |                    |
| Anti-thymocyte globulin                         | [13,24-26]         |
| Alemtuzumab                                     | [29]               |
| IVIG                                            | [30]               |
| Rituximab                                       | [30]               |
| Tacrolimus                                      | [4,13,24,31-34]    |
| Mycophenolate                                   | [9,24,34]          |
| Corticosteroid                                  | [7,33,39]          |
| Other                                           |                    |
| Pregnane X receptor polymorphism NR12           | [35,95]            |
| Donor seropositive                              | [41-43]            |
| Recipient sero-negative                         | [44,96,97]         |
| CMV risk profile                                | [8,24,45]          |
| Paediatric recipient                            | [27]               |
| Advanced donor age                              | [8,13,27,34]       |
| Advanced recipient age                          | [25,32]            |
| Male recipient                                  | [13,34]            |
| African-American recipient                      | [27]               |
| High BMI                                        | [24]               |
| Greater HLA mismatches                          | [7,8,13,27,34]     |
| Prolonged cold ischaemia                        | [8,13]             |
| Delayed graft function                          | [6,13]             |
| Ureteric stent placement                        | [48,49]            |
| Biopsy proven acute rejection                   | [7,24,27]          |
| More recent transplant year                     | [13,14]            |
| Putative protection                             |                    |
The choice of calcineurin inhibitor has a significant impact on risk of BK viral disease. In vitro studies demonstrate cyclosporin has antiviral properties against herpes simplex virus, vaccinia virus and HIV-1 and can inhibit primary BKV infection peak, reactivation and NCCR gene rearrangements in monkey models [31]. Recognition of BK viraemia and BKVAN as a clinical entity has increased dramatically over the past 20 years, a time in which there has been a large-scale adaptation of tacrolimus/mycophenolate-based immunosuppressive regimens compared to cyclosporin/azathioprine [40]. Whilst increasing vigilance and adoption of BKV screening are likely to have contributed to the rise in recognition of BKV-associated problems post-transplant, this observation raises suspicion that the use of tacrolimus and mycophenolate may substantially increase the risk of BKV reactivation. In their open-label, prospective single-centre randomised controlled trial of 200 de-novo adult kidney transplant recipients, Brennan and colleagues reported the highest levels of BK viruria were evident following the combination of tacrolimus and mycophenolate (MPA) and lowest with cyclosporin and MPA but failed to demonstrate a difference in the rates of BK viraemia [32]. The DIRECT trial provides the best evidence to date regarding the differential impact of tacrolimus on BK replication [33]. In this study, 682 kidney transplant recipients received basiliximab as an induction agent, MPA and steroids and were randomised to either tacrolimus or cyclosporin. BK viraemia was more common in recipients that received tacrolimus compared to cyclosporin (16.3% vs. 10.6% at six months (p=0.048) and 12.1% vs. 4.8% at twelve months (p=0.004)). This finding has been replicated in a number of subsequent studies [24] and within US OPTN registry data [13]. Higher BKV titres and higher median BK viral loads were observed within the Tacrolimus arm [33]. The triple combination of tacrolimus, MPA and steroids has been particularly implicated in the development of BKVAN. It is worth noting that cyclosporin interacts with MPA and decreases mycophenolate exposure via reduced entero-hepatic recirculation [36-38]. Therefore, combining tacrolimus and MPA may increase the likelihood of excessive immunosuppression and increase BKVAN risk. Studies employing therapeutic drug monitoring have demonstrated that both high tacrolimus levels (trough levels more than 10ng/ml) and MPA AUC0-12hr more than 50 hr mg/L are particular risk factors for increased immunosuppression and infection with BK virus [24].

### Table 2: Factors associated with increased risk of post-transplant BKV replication and nephropathy.

| Treatment                              | Reference   | Immunosuppression adjustment strategy                              | Study number | Outcome                                      |
|----------------------------------------|-------------|---------------------------------------------------------------------|--------------|----------------------------------------------|
| Immunosuppression discontinuation       | [25,66]     | Discontinuation of CNI or MMF or dose reduction in both             | [35]         | 19/35 maintain allograft function. CNI withdrawal is associated with superior allograft survival compared to dose reduction strategy. |
|                                        | [66]        | Discontinuation of antimetabolite, reduction in CNI for sustained viraemia | [23]         | 12/23 cleared BKV. 5 episodes of acute rejection. No allograft losses. |
| Dose reduction in immunosuppression     | [7]         | Varied; Calcineurin inhibitor dose reduction or conversion          | [6]          | 4 out of 5 patients cleared BKV. 3 episodes of rejection. No allograft losses. |
|                                        | [68]        | Reduction in MMF dose                                               | [22]         | Viremia resolved in 20/22 patients. |
|                                        | [69]        | Initial reduction in CNI followed by discontinuation in MMF         | [38]         | Viremia resolved in 35/38 patients, rejection occurred in 3/35. No allograft losses. |
|                                        | [79]        | Simultaneous dose reduction CNI and MMF                            | [11]         | Viremia resolved in 8/11, 3 episodes of rejection. No allograft loss. |
| Cidofovir                               | [79]        | MMF/CNI reduction with/without “adjuvant” cidofovir                 | [21]         | 6/8 cidofovir patients cleared BKV. 2 acute |

**Table 2:** Factors associated with increased risk of post-transplant BKV replication and nephropathy.
Corticosteroid dose also appears to influence the risk of BKV replication post-transplant. Hirsch and colleagues demonstrated that treatment initiated for acute rejection, and specifically corticosteroid use, was significantly associated with BKV replication and nephropathy [7]. Cumulative steroid dose within the first 7 days of transplantation and until month, also correlate with higher levels of BK viraemia [39].

BKVAN has been uncommonly observed in patients receiving mTOR-based regimens [26]. Observational studies indicate a lower incidence of BK viraemia among patients managed with everolimus containing regimens compared to cyclosporin-based immunosuppression [40]. The US OPTN Registry analysis of [48], 292 kidney transplants demonstrated a lower incidence of PVAN in patients discharged on mTOR-based regimen (1.74% vs. 3.67%) and transplantation of CMV seropositive organs into sero-negative recipients is associated with increased risk of BKVAN [8,24,45]. It has been suggested that CMV serostatus may act as a surrogate marker for immunological risk, and therefore increased immunosuppressive exposure. Interestingly, the incidence of BK viremia in ABO incompatible living donation has been reported as lower than in ABO-compatible transplantation [8] but this finding has been refuted in other studies [46,47]. Certain HLA alleles may specifically modulate risk. Bohl and colleagues demonstrated that the HLA C7 allele may be an important determinant of the ability to control BKV infection and its absence increased the risk of developing BK nephropathy. Other recipient risk factors include dialysis vintage and history of haemodialysis usage [8]. An episode of biopsy proven viremia, the CMV naïve allograft may be inflamed by exposure to CMV sero-positivity and is thus predisposed to other opportunistic viral infections [8].

Along with CMV serostatus, a number of other risk factors for BK viremia and BK nephropathy have been identified and illustrate the complexities of post-transplant immune function. Independent risk factors such pediatric kidney transplant recipient [27] and advanced donor age [8,27] potentially reflect the infective risk associated with immune naivety and immune senescence, respectively. Other risk factors include male recipient, female donor and African-American status [27] and BMI over 30 kg/m² [24], although the explanation for these is less clear. Jacobi and colleagues report that enrolment in a prospective clinical trial appears to be protective for BK viraemia, potentially because of the Hawthorne effect, or alternatively, healthy user bias [8].

The degree of HLA mismatch and HLA sensitisation, (as detected by PRA), are associated with BKV viremia and BKVAN risk [8,27] and may be surrogate markers for immunological risk, and therefore increased immunosuppressive exposure. Interestingly, the incidence of BK viremia in ABO incompatible living donation has been reported as lower than in ABO-compatible transplantation [8] but this finding has been refuted in other studies [46,47]. Certain HLA alleles may specifically modulate risk. Bohl and colleagues demonstrated that the HLA C7 allele may be an important determinant of the ability to control BKV infection and its absence increased the risk of developing sustained viremia by at least 3-fold [42].

Prolonged cold ischaemia [8], delayed graft function [6] and ureteric stent placement [48,49] are associated with increased risk of BK nephropathy. Other recipient risk factors include dialysis vintage and history of haemodialysis usage [8]. An episode of biopsy proven acute rejection is strongly associated with the subsequent development of rejection in cidofovir group. No allograft losses within the cidofovir group. Allograft loss in 9/13 control patients.

Viraemia resolved in 5/11. 1 episode of acute rejection. 1 allograft loss.

Viraemia resolved in 11/21. 4 allograft losses.

No difference in viral load between groups at 1 or 3 months followup.

Significant reduction in BK viral load in all 19 patient. 4 episodes of acute rejection, no allograft loss.

Histological changes resolved in 4/8, viraemia resolved in 4/8, 1 episode of allograft loss.

No change in graft function, viraemia or outcome.

| Treatment | Comparator | Description | Outcome
|-----------|------------|-------------|----------|
| Leflunomide | MMF replaced with leflunomide | [77] | Viraemia resolved in 5/11. 1 episode of acute rejection. 1 allograft loss. |
| | MMF replaced with "low" dose or "high" dose leflunomide | [78] | Viraemia resolved in 11/21. 4 allograft losses. |
| Fluoroquinolone | Levofoxacin vs placebo | [84] | No difference in viral load between groups at 1 or 3 months followup. |
| | Ciprofloxacin and leflunomide progressive therapy and reduction in immunosuppression in a stepwise fashion | [85] | Significant reduction in BK viral load in all 19 patient. 4 episodes of acute rejection, no allograft loss. |
| Human immunoglobulin intravenous | 2g/kg IV over 2-5 days | [87] | Histological changes resolved in 4/8, viraemia resolved in 4/8, 1 episode of allograft loss. |
| | 1.25g/kg as adjuvant to cidofovir | [10] | No change in graft function, viraemia or outcome. |

Table 3: Treatment strategies for BKVAN
of BK viraemia and BKVAN [7,24,27], likely because of intensification of immunosuppression.

**Clinical features of BKV reactivation after transplantation:** Following kidney transplantation, BKV reactivation may manifest in a variety of ways but is usually asymptomatic and frequently accompanied by a rise in serum creatinine. BK viral infection injures uro-epithelium, manifesting as typically painless transplant ureteric stenosis or as painful haemorrhagic cystitis. While a common occurrence following stem cell transplantation, haemorrhagic cystitis secondary to BK virus infection must be differentiated from haemorrhagic cystitis secondary to cyclophosphamide toxicity and adenovirus infection in this patient population. BKV has been infrequently implicated in extra renal pathologies such as pneumonia, encephalitis, hepatitis, retinitis, capillary leak syndrome and malignancy [6].

Biopsy proven acute rejection may coincide with BK virus infection and has emerged as a risk factor for BKVAN and vice versa in a number of studies [8,50]. In their prospective study of renal transplant recipients, Drachenberg and colleagues report concurrence of viral cytopathic changes as well as patchy atrophy and tubulointerstitial changes resembling cellular rejection of borderline or Banff Type I classification [9]. This unfortunate relationship represents a predicament to clinical management of BK viral infection and emphasises the importance of histological diagnosis.

**Immune response to BKV infection:** Innate immune responses are implicated in the host response to BKV. Renal transplant recipients with a high BK viral load exhibit elevated urine levels of IL-1 receptor antagonist protein, IL-3, IL-6 and IL-6 receptor compared with BKV-negative patients [51,52]. This suggests cytokines produced by monocytes and T-helper-2 cells are involved in BKVAN pathogenesis. Anti-BKV CD4+ and CD8+ T cells are implicated in BK clearance and may provide prognostic information. BKV-reactive memory T cells can be detected in both healthy volunteers and kidney transplant recipients. In a recent study, Chen and colleagues used MHC tetramers to detect BKV-reactive T cells in HLA-A’0201 individuals, demonstrating an inverse correlation between the frequency of BKV-reactive CD8+ T cells and BK viral loads in blood and urine [53]. The emergence of virus-reactive IgG antibodies is associated with recovery from BKVAN and BKV clearance in renal transplant recipients in some [54] but not all studies [55].

**Screening and diagnosis:** Low-level BKV reactivation can be detected via the presence of BKV DNA or ‘decoy cells’ in urine [56]. Increasing BKV replication leads to detectable BKV DNA in the peripheral blood, occurring in ~10% of kidney transplant recipients [57]. Persistent BK viraemia is associated with increased risk of BKVAN. The degree of viraemia appears to predict risk of BKVAN with plasma load of ≥10,000 predictive of BK nephropathy [9,58].

In the absence of definitive treatment options, the goal of BK viral screening is to facilitate identification of BKV reactivation at the virucic or vireamic stage with the aim of preventing progression to BKVAN through timely reduction of immunosuppression. Prospective screening studies indicate that BKVAN usually occurs within the first year post-transplantation with a peak in viruria and viraemia detected at around 3 months in 2 European cohort studies [59,57]. International guidelines recommend screening for BKV replication at least every 3 months during the first 2 years post-transplant and annually until the fifth post-transplant year. Adoption of this strategy can identify 80-90% of patients at risk of BKVAN and allow intervention prior to the development of graft dysfunction. More frequent screening intervals have been shown to facilitate earlier diagnosis and potentially better outcomes [57]. There have been no randomised controlled trials of screening and pre-emptive treatment versus treatment following diagnosis of BKVAN.

The optimal screening method for BK virus is not clear. BKV can be detected within urine or blood and screening may adopt either strategy [6]. BK viral shedding in urine is common and may occur in up to 30% of renal transplant recipients [7]. Urine can be assessed for cytological abnormality or by quantification of urine BK DNA by PCR. Testing for BK viruria has the advantages of a high negative predictive value to exclude BK nephropathy, a window period of 6-12 weeks before the onset of viruria and nephropathy, reduced cost and less invasive testing modality [6]. Its use is limited however by the low positive predictive value for PVAN, large physiological fluctuation and delayed reduction in urinary shedding making it inappropriate for monitoring response to therapy [6].

Intense monitoring for BK viruria and viraemia early after transplantation by PCR coupled with prompt reduction in immunosuppression on detection of persistent viraemia has been explored in a study by Brennan and colleagues [32]. The authors report that adoption of this strategy was associated with resolution of BK viraemia and prevented the development of overt BK nephropathy while also avoiding acute rejection and graft loss. Many centres have adopted similar screening protocols based on real-time PCR of plasma, which has a sensitivity approaching 100%, a specificity of ~90%, a positive predictive value of 50% and negative predictive value of 100% for the diagnosis of BK viral infection [60]. The window period from detection of viraemia to progression to BKVAN can be as short as 2-6 weeks, prompting many centres to adopt plasma screening every 1-3 months with a BK viral load of >4 log copies/ml as a trigger to therapeutic intervention [6,60]. As previously mentioned, BK sero-prevalence is common and in unable to discriminate those patients at risk of developing BKVAN. Viral culture has limited utility outside of a research setting. Its use is limited by slow rate of tissue culture and lack of available cell lines [61].

Renal biopsy remains the gold standard for the diagnosis of BKVAN. It is recommended in patients with BKV >4 log copies/ml with or without an elevation in serum creatinine concentration [60]. The histological lesion of BKVAN is characterised by an inflammatory lymphocytic infiltrate that resembles acute cellular rejection. The presence of intra-nuclear BK inclusion bodies which stain positive for the large T antigen or for simian virus 40 is pathognomonic. Biopsy diagnosis can be missed due to sampling error and the patchy nature of histological changes [60]. The false negative rate is about 30% based on a single biopsy core but this improves on repeated sampling [62]. A minimum of two cores is recommended, along with correlation of biopsy results with viruria and viraemia [5,62].

The development of haemorrhagic cystitis or radiological findings of ureteric obstruction should prompt an assessment for BK viruria or viraemia through any of the above mentioned techniques. The presence of BK-induced histological changes is the ureter such as inflammation, epithelial sloughing and fibrosis are necessary to demonstrate causality in the resected ureter.

**Management of BKVAN:** To date there are no antiviral drugs available with specific activity against BKV [31]. There have also been no randomised controlled trials of interventions in BKVAN, such that the evidence underpinning guideline recommendations is limited to...
case series only. Current guidelines recommend timely diagnosis and intervention aimed at improving a patient’s BKV-specific immunity status [6,63,64]. The key management strategy is reduction in immunosuppression, but there is a lack of consensus on the optimal approach. Management approaches can include reduction or discontinuation of the anti-metabolite (MPA or azathioprine), reduction in calcineurin inhibitor dose, or conversion from tacrolimus to cyclosporin (Table 3). There is just one systematic review to date which has evaluated these approaches [65].

In a single centre retrospective analysis, discontinuation of one of three immunosuppressive agents (usually the calcineurin inhibitor) significantly improved 1-year graft survival when compared to dose reduction of all three immunosuppressive agents (87.8% vs. 56.2%; p=0.03) [25]. Antimetabolite withdrawal following detection of BK viraemia has likewise been associated with resolution of BK viraemia while avoiding acute rejection or graft loss in a 5-year follow-up study of a single centre randomised controlled trial [66].

Other studies have evaluated dose reduction in mycophenolate or calcineurin inhibitors and demonstrated efficacy at producing viral clearance following detection of BK viraemia with success rates of 84-96% [7,5,67-69]. International guidelines recommend targeting tacrolimus trough levels to <6ng / mL and cyclosporin trough levels to <150ng /mL although some studies have reported success at levels lower than this [68]. Episodes of acute rejection may following reduction in immunosuppression and appear to be common (8.6-60%), although anecdotaly respond to management with pulse steroids without major impact on graft outcome [7,12,50,67-69]. Judicious reduction in immunosuppression must be accompanied by close monitoring for acute rejection.

Conversion from tacrolimus to cyclosporin has been hypothesised to enhance BK-specific immunity [70]. A recent study demonstrated successful reduction in viraemia or viral clearance with reconstitution of BKV-specific T-cell responses after switching from tacrolimus to cyclosporin, although the change was also accompanied by introduction of cidofovir [71].

The optimal management strategy for recipients who experience persistent BKVAN or BK viraemia despite reduction in immunosuppressive medication is unclear. The role of the immunosuppressant, leflunomide, has been evaluated in a case series [65,72-74] following success in vitro [75]. Leflunomide is usually administered orally as a replacement agent following discontinuation of mycophenolate with careful monitoring of blood counts and liver function tests [6]. Its use is limited by significant toxicity including hepatitis, haemolysis, thrombotic microangiopathy, bone marrow suppression and fungal pneumonia. Therapeutic drug monitoring using active metabolite A771726 (teriflunomide) has been proposed to monitor effective dose of leflunomide and toxicity. In one case series of 22 patients, maintenance of A771726 levels between 50 to 100µg/ml was associated with a reduction in blood and urinary viral load over time [76]. A number of other studies have likewise reported viral clearance and improvement of stabilisation in graft function with leflunomide therapy whilst also documenting a number of adverse events [77,78]. Regrettably the metabolite does not appear to predict toxicity risk [74].

The use of cidofovir has also been investigated in a number of studies. The majority of these studies demonstrate failure to clear viruria or viraemia [10,26,79]. In their analysis of the OPTN/UNOS database, Shah and colleagues concluded that cidofovir therapy did not improve graft survival63. A current randomised placebo-controlled dose escalation study is underway to evaluate safety and efficacy of cidofovir in renal transplant patients with BKVAN.

Fluoro-quinolones can block bacterial DNA replication by inhibiting the bacterial enzymes gyrase and topoisomerase IV. The large T antigen of BKV is likewise reliant upon helicase function for replication and is similarly inhibited by Fluoroquinolones [6,80]. In vitro studies suggest use of quinolone antibiotics inhibits BKV DNA replication [81] and limit viral growth by diminishing the cell release of viral progeny by more than 90% [81,82]. Clinical interest in fluoro-quinolone use for Pneumocystis prophylaxis was associated with lower rates of BK viraemia compared with no fluoro-quinolone use [83]. A similar finding was reported among patients exposed to fluoro-quinolones for other therapeutic indications [83]. A number of small trials have evaluated the role of ciprofloxacin and levofloxacin in BKV infection. In a prospective study of 236 patients the use of prophylactic ciprofloxacin was associated with a lower rate of BKV infection at 3 months but failed to find a difference however at 12 months post transplantation [80]. Mono-therapy with levofloxacin does not significantly improve BK viral load or allograft function when used in addition to overall reduction in immunosuppression [84], suggesting a limited role in established BKVAN6. A regimen utilising ciprofloxacin in combination with leflunomide was associated with a significant decrease in BKV viral load and improved allograft function in a series of 19 kidney transplant recipients [86].

An in vitro study indicated that co-incubation with pooled human immune-globulins inhibited BKV replication in a cell culture model [86]. This observation suggests the presence of neutralising antibodies against BKV in intravenous immunoglobulin (IVIG) preparations. There is limited clinical experience with the use of IVIG in kidney transplant recipients with BKV reactivation. In one study of eight patients with documented BKVAN who received 2g/kg of IVIG over 2-5 days, 4 patients achieved viral eradication, 4 had no evidence of BKVAN on repeat biopsy and 1 graft was lost at mean follow-up of 15 months [87]. The immune-modulatory effect of IVIG has been proposed to be beneficial [6], particularly where there is evidence of synchronous BKVAN and acute cellular rejection [10]. In a study of 12 patients including 10 patients with concomitant BKVAN and acute cellular rejection, IVIG at 1.25g/kg failed to demonstrate a robust improvement in either graft functional stability or resolution of viraemia [10].

In their systematic review of treatment strategies for BK viral infection, Johnston and colleagues report that immunosuppression reduction alone, or in combination with cidofovir results in a death-censored graft rate loss of 8/100 patients-years, which increases to 13/100 patient years when leflunomide is combined with immunosuppression reduction [65]. More established forms of BKVAN nephropathy appear refractory to reductions in immunosuppression alone and require more complex therapeutic approaches, although there is currently inadequate safety and efficacy data to recommend IVIG. This single systematic review highlights the low number of well-conducted randomised controlled trials to inform clinical decisions and reveals the poor quality evidence hampered by case series data, trial heterogeneity, small sample size, brief follow-up as well as publication bias.

Management of BK-associated haemorrhagic cystitis is likewise limited by a paucity of evidence [88]. Management strategies have included cidofovir, hyperbaric oxygen therapy, growth factor instillation and surgical intervention. There is grade B evidence for the
use of MESNA [88]. Antiviral therapy does not appear to reverse ureteric stricture and management of ureteric stenosis relies primarily upon radiologic and/or surgical interventions aimed at relieving the obstruction [32].

Re-transplantation in recipients with BKVAN: Re-transplantation after kidney allograft loss due to BKV has been successfully performed and has greatest chance of success where clearance of BK viremia has been achieved by graft nephrectomy and/or emergence of a BKV-specific immune response, usually facilitated by reduced or discontinued immunosuppression [6,89]. Reported outcomes have been excellent, with graft survival in line with de novo allografts [90]. Nephrectomy alone has not protected against recurrence of BK viral disease [91].

Future research directions: Clinical experience and multiple case series provide clear evidence that reduction in immunosuppression increases viral clearance in kidney transplant recipients with re-activation of BKV. However, the optimal management of recipients with refractory BKVAN is currently unclear. Studies are in progress that with provide further information on the role of leflunomide, fluoro-quinolones, mTOR inhibitors and cidofovir in this setting. It will be important to evaluate the impact of therapies for BKVAN on important patient-level outcomes such as graft survival, and not simply on BK viral load. Additional agents with potential antiviral activity against BK virus are under investigation, including retinoic acid. In vitro studies of retinoic acid demonstrate that this agent may inhibit transcriptional transactivation of the c-fos promoter by polyoma virus and prevents polyoma virus induced transformation [92]. Another important goal is to develop better tools to stratify BKV reactivation risk among kidney transplant recipients. A potential approach is to monitor the frequency of BKV-reactive T cells in the peripheral blood and ongoing studies will evaluate the predictive utility of these assays. A study is already underway evaluating the efficacy and safety of in vitro generated BKV-reactive cytotoxic T cells as a therapy for BKVAN [93]. Currently there is no effective strategy to reduce the risk of BK reactivation post-transplant. Pre-transplant vaccination would be a potential strategy to generate BK immunity in the low number of individuals who are BK sero-negative; although a BK vaccine is not clinically available currently. Furthermore, there are data indicating that the neutralising effect of anti-BK antibodies is serotype specific [94-97]. Therefore, a multivalent BK vaccine would have the potential both to broaden the immune repertoire of BK seropositive individuals, and boost BK-reactive memory cells, potentially reducing the likelihood of BK reactivation.

Conclusions
Reactivation of BKV is common after kidney transplantation and represents an increasing threat to long-term graft survival in the modern transplant era. It is likely that BK viremia is a marker of excessive immunosuppression, and that immune senescence and other donor characteristics interact with recipient and viral factors to manifest the condition. The risk associated with prolonged cold ischaemia, delayed graft function and concomitant or preceding acute rejection suggests a potential role for inflammation as a trigger to viral replication. Choice of induction therapies and anti-rejection regimens clearly contributes to the risk of BKV reactivation. Currently it remains unclear whether any single drug is associated with particularly high risk for BKV, or whether the risk is related to the overall intensity of immunosuppressive therapy. In the absence of specific antiviral strategies, the cornerstone of current management is cautious reduction in immunosuppression and good clinical outcomes are achievable if prompt immunosuppression reduction and aggressive surveillance is adopted. However, established BKVAN appears more refractory to these measures and randomised controlled trials of treatment and prevention strategies are currently needed to guide therapy and improve outcomes in kidney transplant recipients with BKVAN.

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