BK Virus: A Cause for Concern in Thoracic Transplantation?

Authors' Contribution:
Study Design **A**
Data Collection **B**
Statistical Analysis **C**
Data Interpretation **D**
Manuscript Preparation **E**
Literature Search **F**
Funds Collection **G**

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Source of support: Editorial support was funding by Biotest AG, Dreiech, Germany

Human BK polyomavirus (BKV) infection is poorly documented in heart and lung transplant patients. BK viruria and viremia have been estimated to affect 19% and 5% of heart transplant recipients, respectively. Data are limited, especially for lung transplantation, but the proportion of patients progressing from BK viruria to viremia or BKV-related nephropathy (BKVN) appears lower than in kidney transplantation. Nevertheless, a number of cases of BKVN have been reported in heart and lung transplant patients, typically with late diagnosis and generally poor outcomes. Risk factors for BKV infection or BKVN in this setting are unclear but may include cytomegalovirus infection and anti-rejection treatment. The relative infrequency of BKVN or other BK-related complications means that routine BKV surveillance in thoracic transplantation is not warranted, but a diagnostic workup for BKV infection may be justified for progressive renal dysfunction with no readily-identifiable cause; after anti-rejection therapy; and for renal dysfunction in patients with cytomegalovirus infection or hypogammaglobulinemia. Treatment strategies in heart or lung transplant recipients rely on protocols developed in kidney transplantation, with reductions in immunosuppression tailored to match the higher risk status of thoracic transplant patients.

MeSH Keywords: **Heart Transplantation • Lung Transplantation • Polyomavirus**

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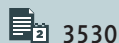
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Background

The importance of human BK polyomavirus (BKV) infection following organ transplantation was first recognized in the mid-1990s, when BKV-related nephropathy (BKVN) was identified as a cause of kidney allograft loss [1,2]. BKV infection is widespread in the general population, affecting more than 80% of individuals [3]. It remains latent, principally in the reno-urinary tract, and is asymptomatic in immunocompetent people despite low-level urinary shedding in up to 10% of individuals [3,4]. Impaired immune surveillance due to chronic immunosuppression therapy, however, can lead to donor- and/or recipient-derived viral reactivation, with asymptomatic high-level urinary BKV viral load (e.g., 10^7 copies/mL) and "decoy" cells detectable on urine cytology. In kidney transplantation, between a half and a third of patients with a high urinary BK viral load (often defined as $\geq 10^7$ copies/mL) and decoy cells progress to BK viremia [5], which, if untreated, can lead to histologic BKVN [4]. BKVN is now estimated to affect between 1% and 10% of kidney transplant recipients [4]. Ureteral obstruction is another, less common, manifestation [4,6]. Nephritis can also develop secondary to BKV reactivation after allogeneic stem cell transplantation; and in that setting, hemorrhagic cystitis is the most common consequence [4,7].

Longitudinal studies from the 1990s and early 2000s documented a stepwise increase in the incidence of BKVN after kidney transplantation [8,9], paralleling the introduction of more intensive immunosuppression regimens [10]. Increased immunosuppression is considered a risk factor for BKV infection [4,11]. Heart and lung transplantation patients receive more intensive immunosuppression than kidney transplant recipients, as well as a higher rate of hypogammaglobulinemia, which incurs an increase in infection risk [12]. Both of these factors would be expected to predispose to BKV infections. BKV monitoring is rare after thoracic transplantation. As a result, relatively few studies regarding BKV infection and its clinical sequelae after heart or lung transplantation have been published, although the number of reported cases is expanding. No trial has explored management options for BKV infection in this setting.

This article considers the available evidence regarding the frequency of BKV infection and its clinical impact following heart or lung transplantation, and considers the options for monitoring and intervention.

Incidence of BKV Infection in Thoracic Transplant Recipients

Heart transplantation

Renal dysfunction is common after heart transplantation [13] due to various contributory factors such as poor kidney function pre-transplant [14], concomitant diabetes [15], and older age [16]. Renal biopsies show diverse histologic patterns [17], but often renal dysfunction is attributed to calcineurin inhibitor-related toxicity. BKV testing is not a routine part of the diagnostic workup. As a result, large-scale studies are lacking and the incidence of BKV infection and BKVN may be underestimated. A recent systematic review pooled data from 305 heart transplant patients enrolled in 8 studies and found the incidence of BK viruria and BK viremia was 19% and 5%, respectively [18] (Figure 1). The reported rates from studies varied considerably. This variation is likely to be at least partly due to different sampling times post-transplantation, but other variables could include the intensity of immunosuppression, use of antiviral prophylaxis, and in some cases, very small study populations that risk having unreliable estimates. For comparison, a large prospective study recently reported BK viruria and viremia in 39.5% and 23.9% of kidney transplant patients at 12 months post-transplantation [20]. Few studies have compared rates of BKV infection across both kidney and heart transplant patients, however, those which have done so reported a similar rate of viruria in both organ types, but a higher rate of viremia after kidney transplantation [21,22].
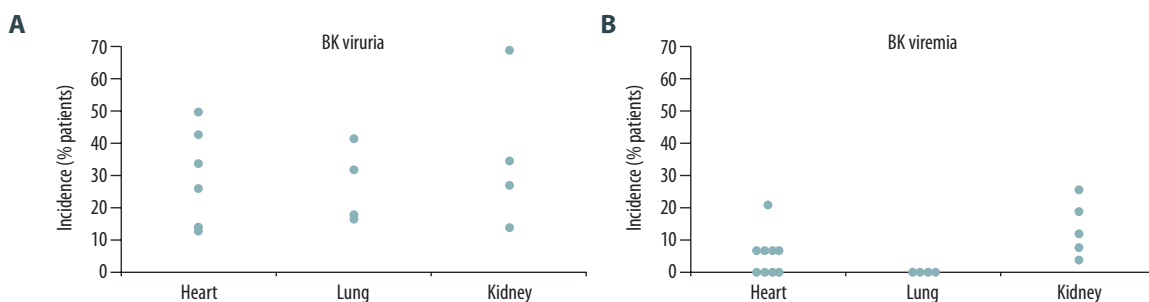

Figure 1. Incidence of (**A**) BK viruria and (**B**) BK viremia in individual studies of heart and lung transplant recipients [18,19]. Each point represents the incidence reported in a single study. Data in kidney transplant patients are shown from studies which compared incidences in both renal and non-renal transplantation, for comparison [18].

Lung transplantation

A few studies have assessed the incidence of BK viruria after lung transplantation, and these studies have included no more than 90 patients [23–26]. The incidence of BK viruria across all 191 patients taking part in these studies was found to be 33% [18], with no cases of BK viremia observed in most studies [23–26]. In 2005, Schwartz et al. retrospectively tested for BKVN in renal biopsy samples from all of the 31 lung transplant recipients who had developed renal impairment at their center over a 5-year period and found only 1 case of BKVN (3%) [27]. Cases of BKVN have been reported [27–30], with instances of associated carcinoma [29,30], and BKV-induced hemorrhagic cystitis [31]. Although larger studies are awaited, the present evidence suggests that although BK viruria is relatively frequent, it only rarely progresses to viremia.

Clinical Effects of BKV Infection in Thoracic Transplantation

Heart transplantation

Conversion from BK viruria to viremia in heart transplant recipients is by no means universal. Pendse et al. found that among 14 adult heart transplant patients with BK viruria, none had viremia [32]. In a prospective study, Loeches and colleagues detected BK viremia in only 5 out of 12 patients with BK viruria over a 1-year follow-up period [33]. Ducharme-Smith et al. documented BK viremia in only 7 out of 28 patients with viruria [19]. Moreover, infections may be transient: only 6 out of the 12 patients with BK viruria in the study by Loeches et al. showed persistent urinary infection, while viremia was persistent in only 2 out of the 5 patients with BKV in serum samples [33].

The presence of BK viruria has not been associated with impaired renal function in prospective [33,34] or retrospective [32] studies in adults [32,33] or children [34]. Neither has BK viremia in adults [21] or children [19] shown a significant association with renal dysfunction in retrospective studies. Overall, out of 398 adults or children assessed for the presence of BKV infection after heart transplantation [19,21,22,26,32,33,35,36], 2 cases of BKVN were identified (0.5%) [19,33].

Published cases of BKVN in adult and pediatric heart transplant patients are summarized in Table 1. The time from transplantation to onset of BKVN ranged from 18 months [39] to 3 years [40] in adults, and from 10 months [45] to 15.7 years [43] in children. Even taking into account a delay between renal dysfunction and diagnosis of BKVN, these timings suggest that BKVN may have a later onset than after kidney transplantation. A prospective study in kidney transplant patients by Hirsch et al.,

for example, found the median time to BKVN to be 28 weeks (range 8 to 86 weeks) [5]. Interestingly, onset of BK viremia appears to be at least as rapid after heart transplantation as in kidney transplant patients. One prospective study of 28 heart transplant patients showed a median time to viremia of 30 days post-transplant [33]), compared to 28 weeks in the prospective trial in kidney transplantation by Hirsch and colleagues [5].

Outcomes after diagnosis of BKVN have varied widely, from stabilization of renal function to dialysis or even death (Table 1).

One case has been published describing a heart transplant patient with urothelial carcinoma who had cytopathic changes consistent with BKV infection and positive staining for polyomavirus large T-antigen in tumor cells [48]. A small number of cases in kidney transplant patients have indicated an association between BKV and bladder cancer [49–52]. Although cases are rare and the mechanism by which BKV could contribute to malignant transformation is unknown, it seems possible that BKV infection may contribute to reno-urinary malignancies in immunocompromised individuals, including thoracic transplant recipients. Renal cell carcinoma and bladder cancer are relatively common in this setting, with one analysis of 6211 heart transplant patients in the USA reporting a 15-year incidence of 3.8% and 3.6%, respectively [53]; an increased risk would be of concern.

Lung transplantation

One prospective longitudinal study of 50 lung transplant patients found mortality to be higher in patients with BK viruria (6/31) than in patients without viruria (0/19), but numbers were small [24]. Three of the deaths were due to chronic graft dysfunction, although the incidence and timing of graft dysfunction was similar in both groups [24]. Viral infection, coronary artery disease, and back surgery accounted for 1 death each; making it difficult to draw any conclusions [24].

Only one research group has assessed the association between BK viruria and renal function [23,24]. They found no significant association between BK viruria or urinary viral load and creatinine clearance [23,24]. However, among a subgroup of 38 patients with at least one urine sample positive for BKV renal function worsened at time points when samples were positive or when there was a 10-fold increase in viral load [23]. The effect of a positive sample remained significant on multivariate analysis. Other studies which investigated the impact of BK infection in non-renal transplant recipients, including lung transplant patients, did not report renal function specifically for the lung transplant subgroups [25,26].

Table 2 summarizes published case reports of BKVN and other BKV-related complications following lung transplantation in adults [27,28,30,54] and children [29,31]. The time to diagnosis

Table 1. Case reports of BKVN and other BKV-related complications in heart transplant recipients.

	Age/gender	Initial maintenance IS	Kidney function at BKVN diagnosis	BV infection* (*time post-tx*)	Initial intervention for BKV	Initial response	Additional intervention for BKV	Outcome
BKVN in adults								
Grahn 2017 [37]	32/male	TAC, MMF, steroids, then low-TAC + EVR; pulse steroids and treatment for ACR + AMR	eGFR 15 mL/min/1.73 m^2 Dialysis required	Viruria ≤1×10^9 Viremia ≤7×10^3 Presumptive BKVN (*11 months*)	TAC dose reduced Leflunomide CMVIG	SCr 141 µmol/L Viruria 2×10^8 Viremia cleared	–	Renal function near normal
Joseph 2015 [38]	63/male	TAC, MMF, steroids	eGFR 33 ml/min/1.73 m^2	Viremia 3×10^6 Florid BKVN on biopsy (*3 years*)	TAC & MMF dose reduced TAC later switched to SIR Ciprofloxacin	Improved viral load (1×10^4) Improved eGFR ACR	i.v. steroids and increased MMF dose for ACR IVIG×8	Dialysis started 2.3 years after BKVN diagnosis
Joseph 2015 [38]	45/male	TAC, MMF, steroids Pulse steroids, rATG and increased MMF for recurrent GCM	eGFR 29 mL/min/1.73 m^2	Viremia 0.8×10^6 Advanced BKVN on biopsy (*2 years*)	TAC, MMF & steroid dose reduced Ciprofloxacin	Improved viral load (1.8×10^5) eGFR improved	None	Acceptable kidney function
Loeches 2011 [33]	57/male	TAC, EVR, steroids	eGFR 57 ml/min/1.73m2	Viruria 8.1×10^8 Viremia 1.1×10^8 Presumptive BKVN (*viruria at 6 months*)	Not stated	Not stated	–	eGFR 51 mL/min/1.73 m^2
Barber 2006 [39]	25/male	TAC, MMF, steroids; later SIR added and TAC reduced	SCr 172 µmol/L	Viruria 8.1×10^8 Viremia 0.5×10^6 BKVN on biopsy) (*18 months*)	TAC stopped, MMF reduced Low-dose cidofovir	Temporary reduction in viremia, renal function deterio-rated	Cidofovir dose increased (2 doses) MMF stopped (leukopenia)	Dialysis Rejection, IS resumed (TAC, MMF, SIR, steroids Low viremia (0.6×10^4)
Limaye 2005 [40]	59/male	TAC, AZA, steroids	SCr 397 µmol/L	BKVN on autopsy (*3 years*)	Patient refused intervention after acute renal failure	–	–	Death
Schmid 2005 [41]	57/male	CsA, AZA, steroids, switched after rejection to TAC, MMF, steroids then SIR started with MMF reduced/stopped	SCr 300 µmol/L	Viruria 10×10^6 Viremia 1–5×10^6 Severe BKVN on biopsy (*2.5 years*)	IS reduced Cidofovir and probenecid (4 months)	SCr improved from 616 to 397 µmol/L	Cidofovir dose reduced	Dialysis started 8 months after BKVN diagnosis

Table 1 cotnnied. Case reports of BKVN and other BKV-related complications in heart transplant recipients.

	Age/gender	Initial maintenance IS	Kidney function at BKVN diagnosis	BV infection* (*time post-tx*)	Initial intervention for BKV	Initial response	Additional intervention for BKV	Outcome
Menahem 2005 [42]	59/female	Initial IS not stated: switched after rejection to TAC, SIR, MMF, steroids, then TAC withdrawn	SCr 280 µmol/L	Viruria 'strongly positive' BKVN on biopsy (*2 years*)	IS reduced to SIR, steroids	SCr increased to 400 µmol/L; still 'strongly positive' viruria	Intermittent low-dose cidofovir	Further renal deterioration (SCr 440 µmol/L) Viruria still 'strongly positive' Restarted dialysis
BKVN in children								
Lorica 2013 [43]	15/male	TAC, AZA, steroids, then low-dose TAC monotherapy following PTLD diagnosis	SCr 203 µmol/L	Viruria>1×10^{10} Viremia 7.6×10^{6} BKVN on biopsy (*15.7 years*)	IVIG x 5 days Cidofovir ×1 dose Ciprofloxacin i.v. steroids for ACR	SCr 264 µmol/L BK viremia decreased to 1.5×10^{6}	Cidofovir x 1	Clinical deterioration & dialysis Death from multiorgan failure 30 days after BKVN diagnosis
Butts 2012 [44]	9/female	TAC (other IS not stated), then TAC reduced, SIR started	158 µmol/L eGFR 20 ml/min/1.73 m_2	Viruria 1.2×10^{10} Viremia 0.5×10^{6} BKVN on biopsy (*8 years*)	Leflunomide for 10 months	BK viremia decreased to 0.1×10^{4} SCr 97 µmol/L	Leflunomide stopped TAC mono-therapy then SIR restarted	Maintained SCr 97 µmol/L at last follow-up (5 months)
Sahney 2010 [45]	7/male	TAC, SIR	eGFR 16 mL/min/1.73 m^2	Viremia 0.2×10^{8} BKVN on biopsy (*10 months*)	IVIG Cidofovir, stopped due to AEs	Viremia persistent	Cidofovofir re-tried but not tolerated TAC reduced Slow decline in viremia	Dialysis
Ali 2010 [46]#	10/male	TAC, MMF; i.v. steroids and increased IS doses following ACR	SCr88 µmol/L	Viruria 7×10^{9} Viremia 3.1×10^{6} BKVN on biopsy (*21 months*)	TAC and MMF reduced Leflunomide	SCr 256 µmol/L Viruria 2.8×10^{9} Viremia 1.7×10^{6}	Cidofovir started	Renal function slightly improved (176 µmol/L) but moderate rejection required i.v. steroids and TAC increase
Pereira 2012 [47]	3/female	TAC, MMF	SCr ~450 µmol/L	Viremia 32×10^{6} BKVN on biopsy (*2 years*)	SIR monotherapy MMF stopped IVIG Cidofovir	SCr increased (547 µmol/L) Viremia persisted at high levels	Increased cidofovir dose, viremia deceased after 1 year (3.3×10^{3})	Invasive BKV CNS disease leading to BKV rhomboencephalitis. Death despite IVIG and increased cidofovir dosing

Table 1 cotniued. Case reports of BKVN and other BKV-related complications in heart transplant recipients.

	Age/gender	Initial IS	Diagnosis	BV infection	Initial interventions	Initial response	Additional intervention	Outcome
Other BKV-related complications								
Lavien 2015 [48]	65/female	TAC, MMF	High-grade urothelial carcinoma	Uninvolved urothelial mucosa showed marked chronic cystitis with typical BKV cytopathic nuclear changes Positive stating for polyomavirus large T-antigen (8 years)	Surgery	–	–	Small bowel obstruction with peritoneal carcinomatosis 12 months post-surgery

* Viruria and viremia shown as copies/mL; # Also reported in reference [19]. ACR – acute cellular rejection; AMR – acute antibody-mediated rejection; AZA – azathioprine; BKVN – BKV nephritis; CMVIG – cytomegalovirus immunoglobulin; CNS – central nervous system; CsA – cyclosporine; eGFR – estimated GFR; EVR – everolimus; GCM – giant cell myocarditis; IS – immunosuppression; VIG – intravenous immunoglobulin; MMF – mycophenolate mofetil; PTLD – post-transplant lymphoproliferative disease; rATG – rabbit antithymocyte globulin; SCr – serum creatinine; SIR – sirolimus; TAC – tacrolimus.

Table 2. Case reports of BKVN and other BK-related complications in lung transplant recipients.

	Age/gender	Initial maintenance IS	Kidney function at BKVN diagnosis	BV infection (*time post-tx to BKVN*)*	Initial intervention for BKV	Initial response	Additional intervention for BKV	Outcome
BKVN								
Kuppachi 2017 [29]	63/male	TAC, AZA, steroids	eGFR 22.3 mL/min/1.73 m^2	Viremia 8.8×10^4 BKVN on biopsy (*2 years*)	AZA stopped, TAC reduced Leflunomide	eGFR declined further (17.7 mL/min/1.73 m^2)	Leflunomide dose increased	Renal function stabilized (eGFR 20.5 mL/min/1.73 m^2) Viremia 1500
Sharma 2013 [54]	30/male	TAC, MMF, steroids	SCr 194 µmol/L	Viremia 3.5×10^6 BKVN on biopsy (*2 years*)	MMF stopped Leflunomide Cidofovir	–	–	SCr 273 µmol/L at 20 months post-diagnosis Viremia 2.6×10^4
Dufek 2013 [30]	8/male	CsA, MMF, steroids then TAC, MMF, steroids	Acute then chronic renal dysfunction, progressing to end-stage renal disease	Viruria >1.0×10^{10} Viruria 1.4×10^8 BKVN on biopsy (*20 months*)	TAC reduced, EVL started, MMF stopped, steroids reduced Cidofovir	BKV load persisted, dialysis started	–	Total nephrectomy

Table 2 continued. Case reports of BKVN and other BK-related complications in lung transplant recipients.

	Age/gender	Initial maintenance IS	Kidney function at BKVN diagnosis	BV infection (*time post-tx to BKVN*)*	Initial intervention for BKV	Initial response	Additional intervention for BKV	Outcome
Egli 2010 [28]	67/female	TAC, MMF, steroids MMF switched to SIR	SCr 183 µmol/L	Viruria 9.9 log10 Viremia 4.6 log10 BKVN on biopsy (*5 years*)	IS reduced Leflunomide for 3 months (stopped due to AEs)	SCr stabilized at 190µmol/L Persistent (7–8 $\log_{10}$) Viremia undetectable	–	Renal and lung function stable
Schwarz 2005 [27]	40/male	TAC, MMF, steroids Bolus steroids for 3 rejections	SCr 380µmol/L	Viruria 1×10^8 Viremia 0.1×10^6 BKVN on biopsy (*15 months*)	No change to IS (recent rejection) Cidofovir (3 courses)	Renal biopsy negative for BKVN Bolus steroids for ACR	Leflunomide started Intermittent increases in viremia	Dialysis started

Other BKV-related complications

	Age/gender	Initial IS	Diagnosis	BV infection	Initial interventions	Initial response	Additional intervention	Outcome
Kuppachi 2017 [29]	63/male	TAC, AZA, steroids	High-grade papillary urothelial carcinoma	Viremia 8.8×10^4 BKV in the bladder cancer (*18 months*)	Intravesicular chemotherapy Surgical intervention	Viremia 0.9×10^6 Hepatic metastases (BKV-positive)	–	Death
Dufek 2013 [30]	8/male	CsA, MMF, steroids then TAC, MMF, steroids	End-stage renal failure (see above) Collecting duct carcinoma	Viruria $>1.0\times10^{10}$ Viruria 1.4×10^8 (*8 months*)	Sunitinib (tyrosine kinase receptor inhibitor) Radiotherapy	–	(No chemotherapy due to general ill health)	Death
Elidemir 2007 [31]	7/female	CsA, MMF, steroids; i.v. steroids for 2 rejections	Hemorrhagic cystitis associated with BKV	Viruria 1.6×10^6 Viremia negative (*7 months*)	No action	–	–	Microscopic hematuria with stable renal function 2 years later (viruria 7.7×10^6)

* Viruria and viremia shown as copies/mL. ACR – acute cellular rejection; AE – adverse events; BKVN – BKV nephritis; CsA – cyclosporine; IS – immunosuppression; MMF – mycophenolate mofetil; SCr – serum creatinine; SIR – sirolimus; TAC – tacrolimus.

of BKVN ranged from 7 months [31] to 2 years post-transplant [27,54]. Kidney function was stabilized in some patients, but others progressed to renal failure.

The literature contains 2 cases in which lung transplant patients also developed BKV-related reno-urinary cancers (urothelial carcinoma and collecting duct carcinoma), both of which were fatal [29,30]. One case of BKV-associated hemorrhagic cystitis has been reported in a pediatric lung transplant recipient; renal function was stable 2 years later without intervention, although microscopic hematuria persisted [31].

Risk Factors for BK Infection and BKVN in Thoracic Transplantation

Various factors are believed to contribute to the risk of BK infection or BKVN, some of which may vary between organ types [10]. A relatively extensive evidence base in kidney transplantation studies has identified numerous risk factors, some of which are specific to kidney recipients, such as HLA-mismatching of the kidney graft and high BK antibody titers in the donor graft (indicative of a high local viral load) [5]. It has also been proposed that subclinical alloimmune activation

in kidney grafts contributes to development of BKVN. Higher HLA mismatch has been shown to be associated with a higher risk of BKVN [55–57] and BKVN-related graft loss [58] after kidney transplantation, although conflicting data exist [59]. Kidney-specific injury associated with poor matching may limit the host's ability to mount an efficient immune response to BKV infection after kidney transplantation, promoting development of BKVN [32]. This would not apply to the native kidneys of thoracic transplant recipients, and native kidneys would not have been subjected to the injury associated with retrieval and ischemia.

Other risk factors identified in kidney transplant patients could potentially apply equally to non-renal transplantation, such as low or no BKV-specific T-cell responses or antibody titers, the potency of immunosuppression, anti-rejection therapy and cytomegalovirus (CMV) infection [5,60–62]. Impaired immune surveillance by CD8 and CD4 T-lymphocytes is, as would be expected, a clear risk factor [63,64], and previous humoral immunity may be protective. There is evidence that BKV-seronegative children are more likely to progress to BKVN after kidney transplantation [65,66]. Information about risk factors after heart or lung transplantation is sparser.

Heart transplantation

In contrast to kidney transplantation [5], no effect of age or gender has been observed in heart transplantation [32,33]. The very limited data available have not demonstrated an effect of different immunosuppressants or exposure levels [32,33], although individual cases have reported where BKVN occurred [37,41,46] or deteriorated [38] after anti-rejection therapy [41]. Non-BKV viral infections may increase risk. Loeches and colleagues found a trend to more frequent CMV infection in patients with BK viruria or viremia (7/13 versus 4/15 without BKV infection, P=0.25) [33], which was comparable with studies from kidney transplantation showing high rates of co-infection [60,61]. In a larger retrospective study of 98 children after heart transplantation, Ducharme-Smith and colleagues found Epstein-Barr virus infection to be associated with BK viruria on multivariate analysis [19]. Regarding an effect of anti-rejection therapy, Razonable et al. found BK viremia in 3 heart transplant patients out of 45 patients tested: all 3 patients had previously been treated for acute rejection (the type of rejection, i.e., humoral or cellular, was not specified) [21]. In a prospective study of 10 pediatric heart patients, 2 of whom developed BK viruria, no demographic or clinical differences were observed between those with or without viremia, but both patients with viremia had a history of acute rejection compared to 4 out of 8 patients free of BKV infection [34].

Lung transplantation

In lung transplantation, Barton et al. found CMV disease and mycophenolate mofetil (MMF) therapy to increase the risk for BK viruria in a series of 23 recipients [25], but in contrast to kidney transplantation [20], they unexpectedly observed a higher rate of BK viruria under cyclosporine therapy compared to tacrolimus therapy. A negative association between acute rejection and subsequent BK viruria was observed in a series of 59 lung transplant patients [23], possibly because of high levels of immunosuppression.

Mammalian Target of Rapamycin (mTOR) Inhibition

One intriguing possibility is that immunosuppression with an mTOR inhibitor may reduce the risk for BKV-related events, based on evidence in kidney transplantation [67]. Evidence is lacking on this issue in thoracic transplantation, but mTOR inhibition has been shown convincingly to lower CMV infection rates after heart transplantation [68] and lung transplantation [69]. Switching from calcineurin inhibitor therapy to an mTOR inhibitor therapy is a relatively frequent approach after heart transplantation and an effect on BKVN could be potentially interesting. However, evidence from kidney transplantation is mixed [70–72], with a recent meta-analysis reporting no conclusive findings [73]. Data regarding a reduced rate of BK infections under mTOR inhibition in heart transplantation are lacking.

Monitoring and Intervention

Urine or plasma screening for BKV replication is recommended for kidney transplant recipients to identify patients at increased risk for BKVN [20]. However, the relatively low rates of conversion to BK viremia and clinical sequelae associated with BK viruria, coupled with the lack of clear risk factors, means that screening is not appropriate in thoracic transplantation. Equally, universal BKV monitoring does not appear justified in the absence of clinical triggers. Instead, questions center on when to test heart and lung transplant recipients for BKV infection in response to clinical events, and when or how to intervene.

Many of the cases of BKVN reported after heart transplantation appeared to represent late diagnosis of BKVN: several patients had advanced disease on biopsy and renal function was often severely compromised by the time of diagnosis [38,41]. Indeed, the case by Limaye et al. was only diagnosed on autopsy [40], with more advanced disease. Published cases are self-selected and it is feasible that more responsive cases have not been equally reported. Nevertheless, this make a good
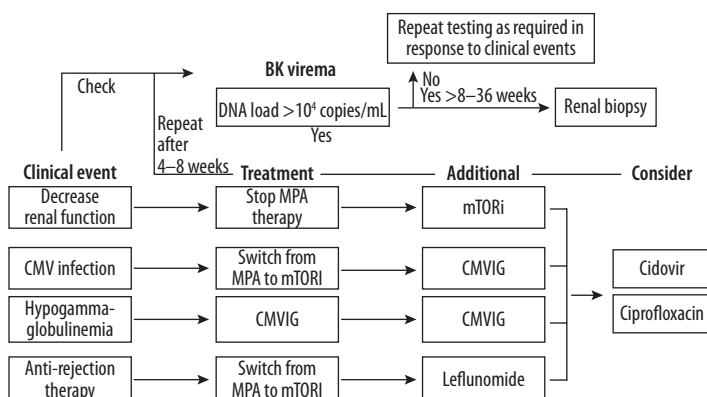
Figure 2. A suggested algorithm for monitoring and diagnosis of BKV infection based on the authors' experience and recommendations in kidney transplantation [4]. CMV – cytomegalovirus; CMVIG – cytomegalovirus immunoglobulin; MPA – mycophenolic acid; mTORi – mammalian target of rapamycin inhibitor.

argument for earlier testing for BKV infection to minimize delays and BK-related histological damage. Where renal dysfunction persists in heart transplant recipients with no easily identifiable cause, such as diabetic nephropathy or calcineurin inhibitor-related nephrotoxicity, BKV polymerase chain reaction (PCR) testing of plasma would seem reasonable. In lung transplant recipients, where BKVN is rarer, testing for BK viremia should still be considered when other causes have been excluded. BK surveillance would also seem justified after use of anti-rejection therapy. Figure 2 presents a suggested algorithm for monitoring and diagnosis of BKV infection in suspected cases after heart and lung transplantation.

The few studies of BKV infection after heart or lung transplantation have not described what intervention, if any, was done after detection of BK viremia [19,23,24,32–34]. In asymptomatic thoracic transplant patients, where BK testing is not usual, it is unlikely that studies on the efficacy of treatments for BK viremia will be undertaken. Experience from kidney transplantation has suggested that BK viremia can be cleared with appropriate management in more than 85% of cases [4]. Even when BKVN has developed, reduced immunosuppression and leflunomide can clear viremia in many patients and improve graft function in at least two-thirds of cases [74–76].

A decision to treat may be made for a patient with deteriorating renal function and high-level BK viremia either without biopsy confirmation of BKVN ("presumptive BKVN") or after biopsy. In the absence of any data regarding optimal intervention for BKVN after heart or lung transplantation, guidelines from kidney transplantation are largely applicable [4]. The mainstay of management is reduction or withdrawal of immunosuppressive drugs [4], an approach supported by one of the very few randomized trials in this area [77]. This is of course problematic if the patient has experienced a previous rejection or if the regimen is already minimized. Occasional incidences of acute rejection have been reported after immunosuppression reduction in response to BKVN [27,38]. Where there is sustained

high-level BK viremia despite reductions in immunosuppression, the addition of antiviral agents is appropriate, including leflunomide, cidofovir, or intravenous immunoglobulin (IVIG) therapy [4]. Published cases of BKVN in heart or lung transplant recipients have typically followed this approach, with reduction or discontinuation of immunosuppressive agents, and introduction of leflunomide, cidofovir, or IVIG in the majority of patients (Tables 1, 2). In contrast to the experience in kidney transplantation [4], outcomes were often unfavorable with frequent requirement for dialysis [38,39,41,42,45,30], surgery [48] or, ultimately, death [29,30,40,43,47] (Tables 1, 2). This is likely to reflect the high viral loads that were present in most cases, with viruria commonly in the range 10^6–10^8 copies/mL and viremia in the range 10^6–10^8 copies/mL. Recently, the antiviral properties of mTOR inhibitors have led to interest in their use, usually with low-dose calcineurin inhibitor therapy, when confronted with a patient with established BKV infection. Evidence from kidney transplantation is conflicting [78], but there are case reports in the literature of successful outcomes with resolution of viremia and preserved allograft function in kidney transplant patients switched from tacrolimus [79] or MMF [80] to everolimus; or patients treated with combined leflunomide and everolimus where reduction of immunosuppression has failed [81]. Switching to everolimus may be an appropriate option after development of BK viremia in heart or lung transplant recipients, although data are awaited.

In one recent case of presumptive BKVN after heart transplantation, CMV immunoglobulin (CMVIG, Cytotect® CP) was initiated because the patient had developed CMV pneumonia [46]. A beneficial effect for Cytotect CP was considered feasible due to verified high levels of BKV binding antibody titers (data on file, Biotest AG, Dreieich, Germany). Neutralizing BKV antibody titers have previously been identified in several available IVIG preparations [82] and would also be expected to be in CMVIG preparations. Leflunomide therapy was started at the same time as CMVIG, coupled with a reduction in tacrolimus trough concentration, and everolimus exposure was
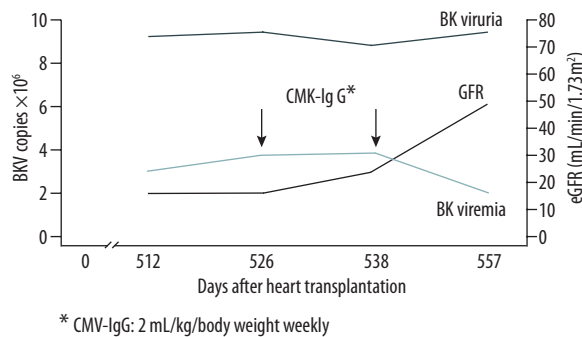
* CMV-IgG: 2 mL/kg/body weight weekly

Figure 3. BK viremia, viruria, and estimated GFR (eGFR) in a 32-year-old heart transplant patient. Medical history was eventful with CMV pneumonia at month 4, and biopsy proven acute cellular rejection (ACR) graded ISHLT 2R at month 6. At month 15, another ACR (ISHLT 2R) occurred, and simultaneously an antibody-mediated rejection (confirmed by donor specific antibodies and low left ventricular ejection fraction) was diagnosed. Intense anti-rejection therapy was started comprising prednisolone pulses, four cycles of plasmapheresis, intravenous immunoglobulin and rituximab. Graft function recovered but renal function deteriorated, and the patient required intermittent dialysis. At month 16 the diagnosis of BK virus nephropathy was made after detection of BK viremia (maximum 1×10^9 copies/mL). From day 512, tacrolimus target trough level was reduced (4–6 ng/mL), everolimus exposure was stabilized (4–6 ng/mL), and leflunomide was started. Additionally, the patient was treated with cytomegalovirus immunoglobulin (CMVIG; cumulative dose 40 000 IE) over 6 weeks. BK viremia cleared, and renal function recovered.

stabilized. In this case, where BKVN was diagnosed rapidly and the serum viral load was relatively low (10^2 copies/mL), renal function was restored to near-normal levels (Figure 3). To our knowledge this is the first case of BKVN being treated with CMVIG after solid organ transplantation, an approach that merits further investigation.

Conclusions

BK viruria occurs in a similar proportion of heart and lung transplant recipients compared to kidney transplant recipients, but viremia appears to be less frequent. Heart transplant patients may be more prone to BK viremia than lung transplant patients, but data are very limited. Progression to BKVN is relatively infrequent compared to kidney transplantation, consistent with the view that organ-specific factors play a role in BK reactivation and progression to renal injury. The cost of routine BK testing in urine or serum is not justified after heart or lung transplantation, but the growing number of case reports describing BKVN or, more rarely describing non-nephrotoxic BKV-associated complications, means that clinicians should be alert to the possibility of BKV-related effects.

An appropriate diagnostic workup for BKV infection may be justified in patients with progressive renal dysfunction after heart or lung transplantation in whom no other cause is readily identifiable. Delayed testing risks progression to advanced, hard-to-treat BKVN. Patients with CMV infection (or CMV disease) are likely to be at higher risk for BKV infection, and renal deterioration in such patients could prompt earlier assessment

for BKV in urine and serum. Heart or lung transplant patients with hypogammaglobulinemia are at increased risk for CMV infection [83] and likely to be more susceptible to BK reactivation, so earlier examination of BK involvement would seem reasonable in these individuals if renal function declines. The clear association between anti-rejection therapy and BKVN in kidney transplantation [5,57,84] would suggest that monitoring of BKV infection after treatment for rejection in heart and lung transplant patients may now also be advisable.

A possible oncogenic effect of BKV infection is being considered based on cases of reno-urinary tumors expressing polyomavirus large T-antigen in kidney transplant patients [85]. An effect seems to emerge only with long-standing BKV infection [85], and in the 3 cases of reno-urinary malignancies reported in thoracic transplant patients (urothelial carcinoma [48], bladder cancer [29] and Duct Bellini cancer [30]) the diagnosis was made between 1.5 [29] and 8 years [48] post-transplant. Although likely to be multifactorial in origin, assessment of BKV infection may be helpful in cases of reno-urinary malignancies after thoracic transplantation.

The rarity of BKVN in heart or lung transplant recipients means that controlled trials of treatment are highly unlikely. Management is likely to follow that advised in kidney transplantation [4], but with the caveat that the minimum exposure levels proposed for kidney transplant patients must be regarded cautiously, and immunosuppressant withdrawal undertaken with care. Greater awareness of the possibility that BKV may be the cause of renal dysfunction may lead to earlier detection and improve chances of viral clearance and renal stabilization.

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