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BK Virus Infection in Renal Allograft Recipients

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1. Introduction

BK virus infection is a challenging complication in renal allograft recipients and has been associated with hematuria, ureteral stenosis, nephropathy and malignancy. BK virus infection occurs early during childhood and the virus lays dormant in uroepithelial cells. Reactivation of the virus in renal transplant recipients is particularly worrisome because of its propensity to cause local damage and incite an inflammatory response leading to acute kidney injury and possible graft loss. Recent, OPTN (Organ Procurement and Transplant Network) registry analysis suggests that the incidence of BK virus related complications are rising and between June 2004 and December 2008, 823 grafts were lost secondary to BK virus related complications [1]. This review will focus on BKV nephropathy (BKVN) in renal allograft recipients.

2. Early history of BKV replication

BK virus (BKV) is a non-enveloped DNA virus that is a member of the polyomavirus family. It shares >70% homology to the other polyomaviruses such as JC virus, a human pathogen, and simian virus 40, an unclear pathogen originally identified in monkeys [2]. BKV was first isolated by Gardner and his colleagues in 1971 from the ureter of a renal transplant recipient who presented with acute renal failure and ureteral stenosis [3]. It was not until 1995, that the second case was identified in the kidney biopsy of a renal allograft recipient at the University of Pittsburgh [4]. In both cases, the patients were treated for rejection prior to detection of the BK virus infection. The case from Pittsburgh illustrates the complexity of this problem. The biopsy of the patient demonstrated virus infection and acute rejection. Attempts at treatment of rejection with steroids only resulted in partial response. This was followed by IVIG therapy and a trial of reduction in immunosuppression. Eighteen weeks following the initial diagnosis, the patient lost his graft. The nephrectomy specimen showed “moderate acute rejection, chronic vascular rejection and scattered viral inclusions.” BKV

replication in immunosuppressed individuals has also been reported to cause native kidney pathology [5-7].

3. Natural history of BKV replication

By the age of 15, greater than 90% of individuals have evidence of past exposure to BKV as detected by BKV specific antibody response. The primary infection is associated with mild symptoms at best, mild upper respiratory infection or mild cystitis. The virus lies dormant in the uroepithelial cells in normal hosts where the intact immune system effectively prevents viral replication. When the host immune system is compromised, the virus, consisting of viral capsid proteins (VP1, VP2 & VP3) and circular double stranded DNA of approximately 5000 base pairs, begins its lytic life cycle [2, 8]. The virus capsid protein, VP1, attaches to the cell membrane via glycoproteins/gangliosides and is endocytosed via caveolae-mediated endocytosis. The virus is then transported to the nucleus where VP2&3 facilitate its entry and the virus utilizes host machinery to facilitate transcription of early and late genes. Early gene proteins, large T antigen, truncated T antigen and small t antigen, facilitate DNA replication and transcription of late genes, virus capsid protein. The virus capsid proteins are synthesized in the cytoplasm and transported back to the nucleus for final virus assembly containing the dsDNA virus copy. Intranuclear assembly of multiple virions causes cell rupture and release of virions into the extracellular space and possible entry into the circulation via peritubular capillaries.

In renal transplant recipients, BKV replication can be detected in the urine within weeks of transplantation. In our studies using BKV VP1 mRNA levels, we found the incidence of BKV replication to be 10% at 1 month, 20% at 3 months, 30% at 6 months which plateaued at 12 month post-transplantation. Similarly other studies identified viruria rates of 19% to 49% within the first year post-transplantation using DNA based assays [9, 10]. Hirsch and colleagues detected BKV replication using decoy cells in the urine in 30% of their study population [11]. Following the detection of viruria, some patients develop viremia. The incidence of BK viremia is less common, varying from 11% to 29% [12, 13]. Viremia is believed to result from a more extensive infection leading to severe tubular injury with rupture of tubular basement membranes and entry of the virus into the blood stream via peritubular capillaries. Ultimately, sustained viremia is associated with BKVN in 1% to 8% of individuals [14]. According to recent analysis of OPTN registry data, the cumulative incidence of BKVN increases from 2% at one year to 3.5% at two years to 6.6% at five years [1].

4. Risk factors for BKV replication and nephropathy

Risk factors for BKV replication and nephropathy include these that affect the recipient's immune response as well as other donor and recipient factors that have been linked through epidemiological studies. Modifiers of the immune response include immunosuppressive therapies, recipient humoral and cellular immunity as well as properties of the virus that may lead to increased virulence and immune evasion. Current data suggest that early

recognition of BKV replication and modulation of immune therapy, allowing for effective recipient response against the virus, would reduce the risk of BKV nephropathy significantly [15]. [Table 1]

Modifiers of Effective Immune Response	Other Risk Factors
1. Therapy affecting immune response	1. Donor graft factors
Induction therapy (ATG)	Seropositive donor
Tacrolimus / MMF combination maintenance therapy	High donor BKV antibody titer
High dose tacrolimus therapy	Greater number of HLA mismatches
Treatment of rejection post-transplantation	Lack of HLA -C7 antigen
Steroid maintenance (triple drug therapy)	Ischemic injury / DGF
2. Recipient immune memory	Placement of ureteral stent
BKV specific humoral immunity / response	2. Recipient factors
BKV specific cellular immunity / response	Older age
3. Virus factors	Male gender
Virulence / Serotype(s)	History of Diabetes
Immune evasion	History of BKVN in previous graft

Table 1. Risk Factors for BKV Nephropathy (BKVN)

ATG, anti-thymocyte globulin; HLA, human leukocyte antigen; DGF, delayed graft function ; Adopted from Medeiros M, Dadhania D, and Velásquez-Jones L, "Nefropatía por virus BK" in *Infecciones en el paciente receptor de trasplante renal* (Alberú J, Morales JL; Publicaciones Permanyer; 2012) In press.

5. Immunosuppressive agents

The intensity of immunosuppression is the major risk factor for BKV replication and subsequent development of BKV nephropathy. Our center performed a prospective study to identify risk factors for BKV replication using BKV VP1 mRNA measurements in the urine and found that ATG induction (OR=5.8; P=0.008) and prednisone maintenance (OR=8.3; P=0.003) were independent risk factors for BKV replication in individuals maintained on tacrolimus and MMF [16]. In addition to potent induction therapies, treatment of acute rejection with steroids was also found to be an independent risk factor for BKV replication and nephropathy[11][17].

Type of maintenance immunosuppressive therapies may be an important risk factor for BKV nephropathy. As evidenced by low acute rejection rates, the combination of tacrolimus and mycophenolate mofetil is currently the most potent combination of maintenance immunosuppressive therapies [18-20]. Brennan and colleagues performed a prospective randomized controlled trial of 200 renal allograft recipients who received either tacrolimus or cyclosporine in combination with azathioprine (AZA) in the low risk group and MMF in the high risk group and found the incidence of BKV replication (viruria and viremia) to be highest in the tacrolimus /MMF combination (46% viruria and 13% viremia) [21].

The dose of maintenance immunosuppressive therapies may also be an important factor. In another retrospective review of 575 renal allograft recipients, Cosio and colleagues evaluated the impact of tacrolimus dose on the incidence of BKV nephropathy [22]. The historical cohort received higher tacrolimus doses (12-15ng/ml in first month, 10-12ng/ml month 1 to 4, 8-10ng/ml month 4 to 12 and then 6-8ng/ml) while the recent cohort received lower tacrolimus doses (10-12ng/ml in first month, 8-10ng/ml month 1-4 and 6-8ng/ml thereafter). The authors found a significantly lower incidence of BKV nephropathy with lower tacrolimus doses (3.6% in the low vs. 12.7% in the high tacrolimus group; $P < 0.001$). In a recent case-controlled analysis of 99 renal allograft recipients (33 cases and 66 controls), the authors found higher tacrolimus levels and prednisone doses during the three months preceding the diagnosis of BKV nephropathy compared to the controls who had undergone a biopsy and did not have BKV nephropathy [23]. They performed random effects logistic modeling and found tacrolimus level ($OR = 1.3$; $P = 0.03$) and prednisone dose ($OR = 1.22$; $P = 0.02$) to be independently associated with BKVN diagnosis. MMF dose was not different between the two groups.

A recent study evaluated the treatment trends for BKV replication in a cohort of 48,292 solitary kidney transplant recipients transplanted from January 2003 to December 2006 [1]. In their analysis, the authors found a rising trend in treatment of BKV replication, corresponding to an increased use of ATG (anti-thymocyte13 globulin) induction therapy and tacrolimus based maintenance immunosuppression. Independent risk factors for BKV replication include ATG induction, tacrolimus, mycophenolate mofetil (MMF) and prednisone maintenance therapies and treatment of acute rejection within the first six months after transplant. In contrast, interleukin 2 receptor (IL-2R) antibody and alemtuzumab induction were not associated with increased incidence of BKV associated treatment. mTOR inhibitor use was associated with a protective effect ($HR = 0.69$; $P = 0.005$) and may be associated with a decreased incidence of BKV nephropathy [1, 24]. In-vitro studies suggest that mTOR inhibitors may inhibit BKV replication via inhibition of large T antigen [25]. A large randomized controlled trial of everolimus with low dose cyclosporine versus MMF with standard cyclosporine dose suggested a lower incidence of BKV viruria and viremia in the everolimus treated group [26]. However, other studies have not demonstrated a protective effect and as a result larger prospective studies are needed to evaluate the role of mTOR inhibitors on BKV replication [18].

6. Recipient humoral and cellular immunity

BKV-specific antibody response may play an important role in the risk for developing BKV nephropathy. Epidemiological studies suggest greater than 90% of adults have been exposed to BK virus during the early years [27] and have measurable humoral immunity. It has also been noted that the antibody titers increase with the development of BKV viremia/nephropathy in the post-transplant period [28]. A study of 70 renal allograft recipients demonstrated that pre-transplant serum anti-BKV IgG titers were lower in patients who went on to develop BKV viremia compared to the 17 patients who never

developed BKV viremia. In those that developed BKV infection, the magnitude of the rise in antibody titer post-transplant correlated with intensity of BKV infection [29]. The same authors demonstrated that the donor BKV seropositive status and the magnitude of the antibody titer was significantly associated with BKV replication in the recipient [30]. Together these data suggest that BKV-specific memory immune response is important for controlling BKV replication and preventing BKV nephropathy especially when the donor has had significant exposure to BKV as measured by BKV antibody titers.

Recent studies have focused on measuring cellular immune response to the BK virus. Similar to the antibody response, BKV specific $\text{INF}\gamma$ secreting T cells increase with the development of BKV viremia. Detection of this cellular immune response early after development of BKV viremia is associated with self-limited BKV infection and the prevention of BKV nephropathy [31, 32]. In addition, tacrolimus therapy inhibits BKV specific T cell immune response and reduction of immunosuppressive therapies does lead to an increase in the BKV specific cellular immune response [33]. Recipients who are not able to increase BKV specific cellular immune response promptly with BKV replication may be at increased risk for nephropathy and kidney damage.

7. Other associated risk factors

Several studies have identified the HLA type of donor and recipient to be important risk factors for BKV nephropathy. Although not all of the studies have found a significant association between HLA mismatches and risk of BKV nephropathy, Awadalla and colleagues found 5-6 HLA mismatches as a significant independent risk factor for BKVN (OR=7.6; $P=0.004$) in a large study cohort ($n=440$) with 40 BKVN patients [34]. Although no association was found with HLA mismatches, Bohl and colleagues found an increased risk of BKVN if the donor lacked HLA-Cw7 allele (RR=3.6; $P=0.008$) [30]. In addition, they also found a significantly increased risk of BKVN with positive donor serostatus for BKV IgG (RR=3.1. $P=0.007$).

Additional recipient risk factors that have been identified are a history of diabetes, older age and male gender [1, 17, 35, 36]. Transplant surgery associated variables such as delayed graft function (DGF), ischemia, deceased donor grafts and use of ureteral stents have also been identified as risk factors for BKV viremia/nephropathy [1, 37, 38].

8. Diagnosis of BKV replication and BKVN

8.1. Noninvasive assays for diagnosis of BKV replication

There are several assays available for the diagnosis of BKV replication in renal allograft recipients. One of the earliest assays was the use of decoy cells in the urine. In this assay urine was examined under the microscope to look for virus infected cells that showed the typical ground glass appearance of the nucleus resulting from intranuclear viral inclusion bodies [39]. Evaluation of "negatively-stained" urine specimens using electron microscopy (EM) identified the typical icosahedral shaped virions [40]. In the current era, the most

commonly used noninvasive assay for diagnosis of BKV replication is urine or plasma BKV DNA copy numbers using real-time quantitative PCR assays.

Our center has developed and validated a noninvasive assay for the diagnosis of BKV replication and BKV nephropathy using urinary cell mRNA assay. In a cohort of 89 patients, urinary cell mRNA levels of BKV VP1 copies above 6.5×10^5 (copies/ng total RNA) diagnosed BKVN with 100% sensitivity and 97% specificity with a positive predictive value of 86% for BKVN [41]. More recently, urinary Haufen was introduced as an accurate predictor of BKVN by a group from the University of North Carolina. Urinary Haufen are “cast-like polyomavirus aggregates” that are detected in the urine using EM [42]. In their investigation, the authors compared the diagnostic utility of current noninvasive tests in clinical practice to urinary Haufen and found that urinary Haufen was associated with the highest specificity and positive predictive value. Table 2 lists the results from this study as well as our center’s study of urinary cell BKV VP1 assay to provide a comprehensive view of all the noninvasive diagnostic assays available for BKVN.

University of North Carolina – Singh et al. JASN 2009					
Test	N	Sensitivity	Specificity	PPV	NPV
Haufen	32	100%	99%	97%	100%
Decoy Cells	32	100%	36%	40%	100%
Urine BKV load – DNA >1,000 K	32	100%	47%	44%	100%
Plasma BKV load >10 K	32	72%	88%	74%	88%
Weill Cornell Medical Center – Dadhania et al. Transplantation 2010					
Test	N	Sensitivity	Specificity	PPV	NPV
Urinary cell BKV VP1 mRNA	88	100%	97%	86%	100%

Table 2. Non-Invasive Diagnosis of BKV Replication
PPV: Positive Predictive Value; NPV: Negative Predictive Value

8.2. Histological diagnosis of BKV nephropathy

Although noninvasive assays are commonly used as a screening tool to identify BKV replication early, the gold standard is still the renal allograft biopsy. The diagnosis of BKVN is made based on the presence of typical viral cytopathic changes in the renal tubular epithelial cells. The presence of BKV is confirmed using an immunohistochemical (IC) staining of the nucleus using an antibody against the large T antigen of SV40 virus which cross reacts with BK and JC viruses [43]. Recently a more sophisticated assay, fluorescence in situ hybridization (FISH) has been developed to identify BK virus within the kidney. In a recent study, a side by side comparison demonstrates no clear advantage of FISH over IC staining [44]. BKVN progresses from early lesions demonstrating normal renal parenchyma

with scattered tubular epithelial cells with BK associated cytopathic changes, to significant tubular damage and an inflammatory response associated with tubulitis, to an advanced lesion where there is considerable tubular atrophy and interstitial fibrosis with chronic inflammation and only scattered cytopathic changes.

A large retrospective review of BKVN associated biopsies performed by the group at the University of Maryland has led the way in developing the diagnostic criteria for different patterns of BKVN [45]. They identified three patterns of histological injury: Pattern A with viral cytopathic changes and almost normal parenchyma, Pattern B with viral cytopathic changes and significant inflammation and tubulitis with varying degrees of interstitial fibrosis and tubular atrophy, and Pattern C with diffuse fibrosis and tubular atrophy associated with some inflammation and very little viral cytopathic changes. Pattern B was divided into B1, B2 & B3 based on the degree of interstitial fibrosis and tubular atrophy. In their evaluation, they noted that Pattern A was associated with 15% risk of graft loss, Pattern B was associated with 25-75% risk of graft loss and Pattern C was associated with >80% risk of graft loss. It is important to note that in their investigation, they also found a 37% discordance rate between two cores of renal allograft tissue obtained from the same biopsy procedure within the same patient, suggesting that the pathological changes can be patchy in nature and a renal allograft biopsy can miss the diagnosis of BKVN.

Recently, the Banff 2009 meeting group has collapsed these patterns into three simple stages – A (early), B (florid) and C (late sclerosing stage) and semiquantified the histological viral loads based on the cytopathic changes. At this time, there are no large studies correlating the use of this system with clinical outcomes [46]. However, a side by side comparison of this schema with an older schema demonstrated no clear advantage of the new staging system compared to the one developed by University of Maryland [47]. Overall, BKVN diagnosis associated with minimal inflammation and minimal scarring has the best prognosis and less than 15% risk of graft loss. The majority of patients with significant inflammation and/or scarring are at risk for persistent allograft dysfunction or progressive decline in renal function.

The presence of the BKV associated cytopathic changes with interstitial inflammation and tubulitis has been the topic of discussion for some time as tubulitis is a hallmark of acute rejection diagnosis. Some support the notion that it represents concurrent acute rejection process within the allograft. However, others feel that it is difficult to separate the anti-viral response from the anti-allograft response. Previous studies suggested that HLA-DR staining of renal allograft would distinguish BKVN with rejection from BKVN alone. However, these data have not been validated in subsequent studies and HLA-DR staining is not used routinely to identify concurrent acute rejection [48, 49]. In patients with BKVN, renal tubules with intense cytopathic changes demonstrated positive C4d staining of the tubular basement membrane but not in peritubular capillaries. In a study of 113 biopsies of renal allograft from recipients with BKV replication, PTC (peritubular capillary) C4d staining was found to be a valid marker for antibody mediated rejection [50]. In patients with BKVN, renal tubules with intense cytopathic changes demonstrated positive C4d staining of the tubular basement membrane but not in peritubular capillaries.

The makeup of cellular infiltration in a renal allograft with BKVN is very similar to those with acute rejection [51]. Our group feels it is difficult to distinguish the anti-viral cellular response from the anti-allograft cellular response. Using the urinary cell mRNA profiles, we found that the granzyme B mRNA levels of BKVN patients were heterogeneous [41]. Those with poor graft function following BKVN had levels that were similar to those with acute rejection while those with stable function had granzyme B mRNA levels that were similar to stable patients with normal protocol biopsies. Furthermore, we found a positive relationship between elevated granzyme B levels and the risk for decline in graft function and a trend towards increased graft loss in individuals with the highest levels of urinary cell granzyme B mRNA.[Figure1]

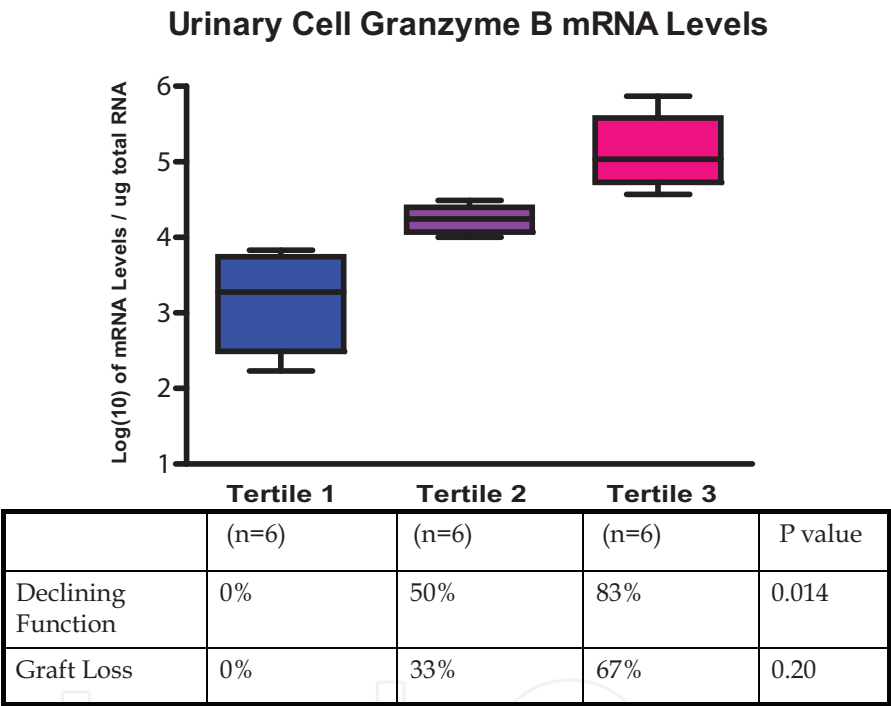


Figure 1. Baseline Urinary Cell Granzyme B mRNA Levels Predict Graft Function in BKVN
Data derived from original study published by Dadhania et al. in *Transplantation* 2010;90(2):189-97

9. Management of BKV replication and BKVN

Routine monitoring of BKV replication is essential for the prevention of BKVN and improving renal allograft outcomes in individuals with BKVN. BKV infection progresses in stages, from viruria to viruria+viremia to viruria+viremia+nephropathy to graft loss. To prevent progression to nephropathy, intervention should begin at the stage of significant viruria and/or viremia. Intervention in this early stage prior to development of BKVN has been termed “preemptive” strategy and generally involves stepwise reduction in immunosuppressive therapies [15].

9.1. Preemptive reduction in immunosuppressive therapies

In the current era, noninvasive monitoring for BKV replication has become a routine practice. Most centers have developed thresholds for initiating preemptive reduction in immunosuppressive therapies in the hopes of preventing BKVN. In a prospective study of 62 renal allograft recipients, Ginevri and colleagues found the incidence of viruria to be 64% and viremia 22%. Of the 13 individuals with viremia (2,460 to 170,000 copies/ml), 100% had clearance of viremia by median of 2 months follow up [52]. In another study of 123 patients, 13 developed viremia in which 2 had evidence of BKVN and the remaining 11 did not. With reduction in immunosuppression, 10 of 11 patients without BKVN had clearance of viremia by median of 5 months follow up [10]. Schaub and colleagues evaluated the impact of a three step protocol for reduction in immunosuppression in patients with viremia, presumptive BKVN and biopsy confirmed BKVN. In their study, step 1 was reduction in tacrolimus to target trough of 6-8ng/ml, step 2 was further reduction in tacrolimus to 4-6ng/ml and step 3 was 50% reduction in MMF (mycophenolate mofetil). In their prospective study of 206 patients, they found step 1 cleared viremia in 100% of patients (n=8) with less than 10,000 copies/ml of BKV, 47% (8/17) of those with presumptive BKVN (>10,000 copies/ml of BKV) and 15% (2/13) of those with BKVN. Step 1 & 2 cleared BKV viremia in 88% (15/17) of those with presumptive BKVN and 61% (8/13) of those with BKVN. Finally, Step 1,2&3 cleared BKV viremia in 92% of individuals with biopsy proven BKVN. However, they found the incidence of acute rejection (subclinical + clinical) to be 24% in those with presumptive BKVN and 38% in those with biopsy proven BKVN [49]. These data suggest that even with systematic monitoring for BKV viremia, a small percentage of patients will present with biopsy confirmed BKVN and clearance of BKV viremia is achieved easily in those with low copies of BKV. In those with high copies of BKV or presumptive BKVN, clearance of BK viremia is possible with systematic reduction in immunosuppressive therapies but at the expense of subclinical or clinical acute rejection episodes. As a result, patients who develop BKV viremia should be monitored closely, not only during the viremic phase but also after clearance of viremia.

10. Management of biopsy confirmed BKVN

The cornerstone of managing patients with BKVN is reduction in immunosuppressive therapies. However this strategy is associated with increased risk of acute rejection episodes and shorter graft survival times. Vasudev and colleagues evaluated their experience with BKVN by dividing their cohort into those recipients who did not have screening for BKV replication (n=16) and those who were diagnosed with BK viremia and subsequently found to have BKVN on biopsy (n=25). Renal allograft recipients were managed with reduction in immunosuppressive therapies and they found a three year actuarial graft survival rate of 58%. In those who retained their grafts, the stabilization of renal function correlated with reduction in calcineurin inhibitors.

The optimal management for those individuals that have BKVN with tubulitis is unclear. University of Pittsburgh performed a retrospective evaluation of individuals with BKVN

and tubulitis who received initial increase in immunosuppression (pulse steroids) followed by reduction in immunosuppression, reduction in immunosuppression only and no change in immunosuppression. In their study, reduction in immunosuppression compared to pulse steroids was associated with reduction in cytopathic changes (83% vs. 20%; $P=0.004$) [53]. Pulse steroids did result in greater improvement in tubulitis (55% vs. 26%) but this effect was not associated with improvement in renal function. Reduction in immunosuppression resulted in lower rates of graft loss in individuals with BKVN and clearance of viremia was associated with improved graft survival (46% vs. 25%) [47]. However, greater than 30-50% of individuals continue to have significant decrease in renal function [54].

IVIg has also been used to manage BKV replication because of its anti-inflammatory activity as well as the presence of humoral immunity to BKV [55, 56]. Studies indicate that treatment with IVIg in combination with reduction in immunosuppression is associated with clearance of viremia and histological clearance. Recently, a case report suggested that the use of IVIg was associated with increase in BKV copies [57]. Since IVIg has anti-inflammatory properties, it is possible that use of IVIg is actually associated with an increase in total immunosuppression and thus results in a rise in BKV. To evaluate the use of IVIg as an anti-inflammatory agent that does not result in an increase in BKV replication requires controlled prospective trials.

To date there are no antiviral drugs that have been proven to effectively inhibit BKV replication and associated graft damage. Various antivirals as well as anti-inflammatory agents have been used for management of BKVN in single center studies and have been reviewed by Rinaldo and Hirsch [58]. Cidofovir, a nucleoside analogue used for treatment of numerous viruses, has been used for management of BKV replication in HSCT (hematopoietic stem cell transplant) recipients as well in those with kidney transplants [59]. Treatment with cidofovir is limited by its potential for nephrotoxicity and currently, a newer agent that is a lipid conjugate of cidofovir, CXM001, is being studied for management of BKV associated hemorrhagic cystitis and BKVN [60]. Fluoroquinolones, anti-bacterial drug that inhibits DNA gyrase, have also been suggested to have activity against BK virus. Single center studies suggest that use of fluoroquinolones do result in decrease BKV replication [61]. However, its use in the management of BKVN has not been prospectively studied.

In addition to anti-viral/anti-bacterial agents, agents with immunosuppressive properties have also been used to inhibit BKV replication. Leflunomide, an anti-inflammatory agent used in rheumatoid arthritis, is another agent whose metabolite inhibits protein kinase activity and pyrimidine synthesis. This drug has been shown to reduce BKV replication in some studies and the efficacy is linked to achieving drug levels above 40ug/ml. However, there are no randomized controlled trials demonstrating its effectiveness and it has been associated with significant liver toxicity. FK778 is a drug that is closely related to the active metabolite of leflunomide. A phase 2 randomized controlled trial that compared MMF or FK778 based maintenance immunosuppression did not demonstrate a benefit in preventing BK viremia or viremia [62]. Epidemiological studies also suggest that rapamycin, a maintenance immunosuppressive agent, may be associated with lower incidence of BKV

replication. Preliminary data suggests that initiation of rapamycin to manage BKV replication may be associated with faster clearance of BKV viremia [63]. Larger studies are necessary to clarify the role of rapamycin in the management of BKVN.

When the patient presents with BKVN, one is obligated to intervene to avoid progression to graft loss. At this time, the main strategy that is employed for BKVN is reduction in immunosuppression. Johnston and colleagues pooled all the existing data on three different strategies to manage BKVN - reduction in immunosuppressive therapies (IS) alone versus cidofovir plus reduction in IS versus leflunomide with reduction in IS [64]. They found that the graft failure rate was not significantly different between the three groups. They concluded that there is no convincing evidence that the use of adjuvant therapies provides additional benefit to reduction in IS alone for management of BKVN patients.

11. Re-transplantation in renal allograft recipients with BKVN

Most reports indicate that risk of graft loss and persistent graft dysfunction following BKVN diagnosis is high [47]. Having suffered a graft loss, many of these patients return to the wait list with higher PRA (panel reactive antibodies) and as a result wait longer for a kidney transplant [65]. However, graft loss due to BKVN is not a contraindication to re-transplantation. The most important factor in preventing BKVN in the subsequent graft is clearance of BKV viremia/viruria prior re-transplantation [66]. Furthermore, at this time there are no recommendations for avoiding any specific immunosuppressive therapy at the time of subsequent transplant. Most recipients with failed graft due to BKVN have been re-transplanted with the centers' standard immunosuppressive protocols. Of the 126 individuals who underwent re-transplantation following graft loss attributable to BKV, BKV replication occurred in 17% with only 1 graft loss attributable to BKVN [65].

12. Summary

BKV infection and development of BKVN in renal allograft recipients is a growing concern given the use of more potent immunosuppressive agents. The lack of effective anti-viral therapy for BKV results in a challenging management problem for transplant physicians. At this time, data suggest that prevention of BKVN through prospective monitoring and preemptive reduction in immunosuppression is a reasonable approach. Laskin and colleagues suggested that viruria measurement every 3 months followed by viremia measurement if viruria is detected is as cost-effective as viremia monitoring every 3 months. Patients with BKV replication or nephropathy should be monitored very closely (every two weeks) until viremia has cleared. Persistent viremia should lead to a kidney biopsy to assess the histological stage of BKV and to determine prognosis.

The risk of graft loss remains high in individuals with BKVN and concurrent inflammation. There is an urgent need for randomized controlled trials to evaluate novel therapies and their potential advantage over reduction in immunosuppressive therapies alone. In addition, development and validation of noninvasive biomarkers to monitor BKV

replication and associated inflammatory response are necessary to enhance the management of allograft recipients with BKVN.

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13. References

- [1] Dharnidharka VR, Cherikh WS, Abbott KC. An OPTN analysis of national registry data on treatment of BK virus allograft nephropathy in the United States. *Transplantation* 2009; 87 (7): 1019.
- [2] van Aalderen MC, Heutinck KM, Huisman C, ten Berge IJ. BK virus infection in transplant recipients: clinical manifestations, treatment options and the immune response. *Neth J Med*; 70 (4): 172.
- [3] Gardner SD, Field AM, Coleman DV, Hulme B. New human papovavirus (B.K.) isolated from urine after renal transplantation. *Lancet* 1971; 1 (7712): 1253.
- [4] Purighalla R, Shapiro R, McCauley J, Randhawa P. BK virus infection in a kidney allograft diagnosed by needle biopsy. *Am J Kidney Dis* 1995; 26 (4): 671.
- [5] Crum-Cianflone N, Quigley M, Utz G, Hale B. BK virus-associated renal failure among HIV patients. *AIDS* 2007; 21 (11): 1501.
- [6] Egli A, Helmersen DS, Taub K, Hirsch HH, Johnson A. Renal failure five years after lung transplantation due to polyomavirus BK-associated nephropathy. *Am J Transplant*; 10 (10): 2324.
- [7] O'Donnell PH, Swanson K, Josephson MA, et al. BK virus infection is associated with hematuria and renal impairment in recipients of allogeneic hematopoietic stem cell transplants. *Biol Blood Marrow Transplant* 2009; 15 (9): 1038.
- [8] Randhawa P, Brennan DC. BK virus infection in transplant recipients: an overview and update. *Am J Transplant* 2006; 6 (9): 2000.
- [9] Babel N, Fendt J, Karaivanov S, et al. Sustained BK viremia as an early marker for the development of BKV-associated nephropathy: analysis of 4128 urine and serum samples. *Transplantation* 2009; 88 (1): 89.
- [10] Almeras C, Foulongne V, Garrigue V, et al. Does reduction in immunosuppression in viremic patients prevent BK virus nephropathy in de novo renal transplant recipients? A prospective study. *Transplantation* 2008; 85 (8): 1099.

- [11] Hirsch HH, Knowles W, Dickenmann M, et al. Prospective study of polyomavirus type BK replication and nephropathy in renal-transplant recipients. *N Engl J Med* 2002; 347 (7): 488.
- [12] Agha I, Brennan DC. BK virus and immunosuppressive agents. *Adv Exp Med Biol* 2006; 577: 174.
- [13] Bressollette-Bodin C, Coste-Burel M, Hourmant M, Sebille V, Andre-Garnier E, Imbert-Marcille BM. A prospective longitudinal study of BK virus infection in 104 renal transplant recipients. *Am J Transplant* 2005; 5 (8): 1926.
- [14] Hirsch HH, Brennan DC, Drachenberg CB, et al. Polyomavirus-associated nephropathy in renal transplantation: interdisciplinary analyses and recommendations. *Transplantation* 2005; 79 (10): 1277.
- [15] Ramos E, Drachenberg CB, Wali R, Hirsch HH. The decade of polyomavirus BK-associated nephropathy: state of affairs. *Transplantation* 2009; 87 (5): 621.
- [16] Dadhania D, Snopkowski C, Ding R, et al. Epidemiology of BK virus in renal allograft recipients: independent risk factors for BK virus replication. *Transplantation* 2008; 86 (4): 521.
- [17] Prince O, Savic S, Dickenmann M, Steiger J, Bubendorf L, Mihatsch MJ. Risk factors for polyoma virus nephropathy. *Nephrol Dial Transplant* 2009; 24 (3): 1024.
- [18] Gralla J, Wiseman AC. Tacrolimus/sirolimus versus tacrolimus/mycophenolate in kidney transplantation: improved 3-year graft and patient survival in recent era. *Transplantation* 2009; 87 (11): 1712.
- [19] Johnson C, Ahsan N, Gonwa T, et al. Randomized trial of tacrolimus (Prograf) in combination with azathioprine or mycophenolate mofetil versus cyclosporine (Neoral) with mycophenolate mofetil after cadaveric kidney transplantation. *Transplantation* 2000; 69 (5): 834.
- [20] Vacher-Coponat H, Moal V, Indreies M, et al. A randomized trial with steroids and antithymocyte globulins comparing cyclosporine/azathioprine versus tacrolimus/mycophenolate mofetil (CATM2) in renal transplantation. *Transplantation*; 93 (4): 437.
- [21] Brennan DC, Agha I, Bohl DL, et al. Incidence of BK with tacrolimus versus cyclosporine and impact of preemptive immunosuppression reduction. *Am J Transplant* 2005; 5 (3): 582.
- [22] Cosio FG, Amer H, Grande JP, Larson TS, Stegall MD, Griffin MD. Comparison of low versus high tacrolimus levels in kidney transplantation: assessment of efficacy by protocol biopsies. *Transplantation* 2007; 83 (4): 411.
- [23] Manitpisitkul W, Drachenberg C, Ramos E, et al. Maintenance immunosuppressive agents as risk factors for BK virus nephropathy: a case-control study. *Transplantation* 2009; 88 (1): 83.
- [24] Benavides CA, Pollard VB, Mauiyyedi S, Podder H, Knight R, Kahan BD. BK virus-associated nephropathy in sirolimus-treated renal transplant patients: incidence, course, and clinical outcomes. *Transplantation* 2007; 84 (1): 83.

- [25] Liacini A, Seamone ME, Muruve DA, Tibbles LA. Anti-BK virus mechanisms of sirolimus and leflunomide alone and in combination: toward a new therapy for BK virus infection. *Transplantation*; 90 (12): 1450.
- [26] Tedesco Silva H, Jr., Cibrik D, Johnston T, et al. Everolimus plus reduced-exposure CsA versus mycophenolic acid plus standard-exposure CsA in renal-transplant recipients. *Am J Transplant*; 10 (6): 1401.
- [27] Stolt A, Sasnauskas K, Koskela P, Lehtinen M, Dillner J. Seroepidemiology of the human polyomaviruses. *J Gen Virol* 2003; 84 (Pt 6): 1499.
- [28] Hariharan S, Cohen EP, Vasudev B, et al. BK virus-specific antibodies and BKV DNA in renal transplant recipients with BKV nephritis. *Am J Transplant* 2005; 5 (11): 2719.
- [29] Bohl DL, Brennan DC, Ryschkewitsch C, Gaudreault-Keener M, Major EO, Storch GA. BK virus antibody titers and intensity of infections after renal transplantation. *J Clin Virol* 2008; 43 (2): 184.
- [30] Bohl DL, Storch GA, Ryschkewitsch C, et al. Donor origin of BK virus in renal transplantation and role of HLA C7 in susceptibility to sustained BK viremia. *Am J Transplant* 2005; 5 (9): 2213.
- [31] Comoli P, Hirsch HH, Ginevri F. Cellular immune responses to BK virus. *Curr Opin Organ Transplant* 2008; 13 (6): 569.
- [32] Schachtner T, Muller K, Stein M, et al. BK virus-specific immunity kinetics: a predictor of recovery from polyomavirus BK-associated nephropathy. *Am J Transplant*; 11 (11): 2443.
- [33] Egli A, Kohli S, Dickenmann M, Hirsch HH. Inhibition of polyomavirus BK-specific T-Cell responses by immunosuppressive drugs. *Transplantation* 2009; 88 (10): 1161.
- [34] Awadalla Y, Randhawa P, Ruppert K, Zeevi A, Duquesnoy RJ. HLA mismatching increases the risk of BK virus nephropathy in renal transplant recipients. *Am J Transplant* 2004; 4 (10): 1691.
- [35] Trofe J, Gaber LW, Stratta RJ, et al. Polyomavirus in kidney and kidney-pancreas transplant recipients. *Transpl Infect Dis* 2003; 5 (1): 21.
- [36] Ramos E, Drachenberg CB, Papadimitriou JC, et al. Clinical course of polyoma virus nephropathy in 67 renal transplant patients. *J Am Soc Nephrol* 2002; 13 (8): 2145.
- [37] Siparsky NF, Kushnir LF, Gallichio MH, Conti DJ. Ureteral stents: a risk factor for polyomavirus BK viremia in kidney transplant recipients undergoing protocol screening. *Transplant Proc*; 43 (7): 2641.
- [38] Thomas A, Dropulic LK, Rahman MH, Geetha D. Ureteral stents: a novel risk factor for polyomavirus nephropathy. *Transplantation* 2007; 84 (3): 433.
- [39] Nicleleit V, Klimkait T, Binet IF, et al. Testing for polyomavirus type BK DNA in plasma to identify renal-allograft recipients with viral nephropathy. *N Engl J Med* 2000; 342 (18): 1309.
- [40] Howell DN, Smith SR, Butterly DW, et al. Diagnosis and management of BK polyomavirus interstitial nephritis in renal transplant recipients. *Transplantation* 1999; 68 (9): 1279.

- [41] Dadhania D, Snopkowski C, Ding R, et al. Validation of noninvasive diagnosis of BK virus nephropathy and identification of prognostic biomarkers. *Transplantation*; 90 (2): 189.
- [42] Singh HK, Andreoni KA, Madden V, et al. Presence of urinary Haufen accurately predicts polyomavirus nephropathy. *J Am Soc Nephrol* 2009; 20 (2): 416.
- [43] Drachenberg CB, Hirsch HH, Ramos E, Papadimitriou JC. Polyomavirus disease in renal transplantation: review of pathological findings and diagnostic methods. *Hum Pathol* 2005; 36 (12): 1245.
- [44] Wang Z, Portier BP, Hu B, et al. Diagnosis of BK viral nephropathy in the renal allograft biopsy: role of fluorescence in situ hybridization. *J Mol Diagn*; 14 (5): 494.
- [45] Drachenberg CB, Papadimitriou JC, Hirsch HH, et al. Histological patterns of polyomavirus nephropathy: correlation with graft outcome and viral load. *Am J Transplant* 2004; 4 (12): 2082.
- [46] Sar A, Worawichawong S, Benediktsson H, Zhang J, Yilmaz S, Trpkov K. Interobserver agreement for Polyomavirus nephropathy grading in renal allografts using the working proposal from the 10th Banff Conference on Allograft Pathology. *Hum Pathol*; 42 (12): 2018.
- [47] Masutani K, Shapiro R, Basu A, Tan H, Wijkstrom M, Randhawa P. The Banff 2009 Working Proposal for polyomavirus nephropathy: a critical evaluation of its utility as a determinant of clinical outcome. *Am J Transplant*; 12 (4): 907.
- [48] Nickleit V, Hirsch HH, Zeiler M, et al. BK-virus nephropathy in renal transplants-tubular necrosis, MHC-class II expression and rejection in a puzzling game. *Nephrol Dial Transplant* 2000; 15 (3): 324.
- [49] Schaub S, Hirsch HH, Dickenmann M, et al. Reducing immunosuppression preserves allograft function in presumptive and definitive polyomavirus-associated nephropathy. *Am J Transplant*; 10 (12): 2615.
- [50] Batal I, Zainah H, Stockhausen S, et al. The significance of renal C4d staining in patients with BK viruria, viremia, and nephropathy. *Mod Pathol* 2009; 22 (11): 1468.
- [51] Rogers NM, Russ GR, Cooper J, Coates PT. Immunophenotyping of interstitial infiltrate does not distinguish between BK virus nephropathy and acute cellular rejection. *Nephrology (Carlton)* 2009; 14 (1): 118.
- [52] Ginevri F, Azzi A, Hirsch HH, et al. Prospective monitoring of polyomavirus BK replication and impact of pre-emptive intervention in pediatric kidney recipients. *Am J Transplant* 2007; 7 (12): 2727.
- [53] Celik B, Shapiro R, Vats A, Randhawa PS. Polyomavirus allograft nephropathy: sequential assessment of histologic viral load, tubulitis, and graft function following changes in immunosuppression. *Am J Transplant* 2003; 3 (11): 1378.
- [54] Wadei HM, Rule AD, Lewin M, et al. Kidney transplant function and histological clearance of virus following diagnosis of polyomavirus-associated nephropathy (PVAN). *Am J Transplant* 2006; 6 (5 Pt 1): 1025.
- [55] Sbrana S, Ruocco L, Vanacore R, Azzara A, Ambrogi F. In vitro effects of an immunoglobulin preparation for intravenous use (IVIg) on T-cells activation. *Allerg Immunol (Paris)* 1993; 25 (1): 35.

- [56] Sener A, House AA, Jevnikar AM, et al. Intravenous immunoglobulin as a treatment for BK virus associated nephropathy: one-year follow-up of renal allograft recipients. *Transplantation* 2006; 81 (1): 117.
- [57] Maggiore U, Medici MC, Vaglio A, Buzio C. Increased viral load after intravenous immunoglobulin therapy for BK virus-associated nephropathy. *Transpl Infect Dis*; 12 (5): 470.
- [58] Rinaldo CH, Hirsch HH. Antivirals for the treatment of polyomavirus BK replication. *Expert Rev Anti Infect Ther* 2007; 5 (1): 105.
- [59] Araya CE, Lew JF, Fennell RS, Neiberger RE, Dharnidharka VR. Intermediate dose cidofovir does not cause additive nephrotoxicity in BK virus allograft nephropathy. *Pediatr Transplant* 2008; 12 (7): 790.
- [60] Gosert R, Rinaldo CH, Wernli M, Major EO, Hirsch HH. CMX001 (1-O-hexadecyloxypropyl-cidofovir) inhibits polyomavirus JC replication in human brain progenitor-derived astrocytes. *Antimicrob Agents Chemother*; 55 (5): 2129.
- [61] Chandraker A, Ali S, Drachenberg CB, et al. Use of fluoroquinolones to treat BK infection in renal transplant recipients. *American Journal of Transplantation* 2004; 4: 587.
- [62] Guasch A, Roy-Chaudhury P, Woodle ES, Fitzsimmons W, Holman J, First MR. Assessment of efficacy and safety of FK778 in comparison with standard care in renal transplant recipients with untreated BK nephropathy. *Transplantation*; 90 (8): 891.
- [63] Sanchez Fructuoso AI, Calvo N, Perez-Flores I, et al. Mammalian target of rapamycin signal inhibitors could play a role in the treatment of BK polyomavirus nephritis in renal allograft recipients. *Transpl Infect Dis*; 13 (6): 584.
- [64] Johnston O, Jaswal D, Gill JS, Doucette S, Fergusson DA, Knoll GA. Treatment of polyomavirus infection in kidney transplant recipients: a systematic review. *Transplantation*; 89 (9): 1057.
- [65] Dharnidharka VR, Cherikh WS, Neff R, Cheng Y, Abbott KC. Retransplantation after BK virus nephropathy in prior kidney transplant: an OPTN database analysis. *Am J Transplant*; 10 (5): 1312.
- [66] Geetha D, Sozio SM, Ghanta M, et al. Results of repeat renal transplantation after graft loss from BK virus nephropathy. *Transplantation*; 92 (7): 781.