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Review

BK Virus-Associated Nephropathy in Adult Patients Post Kidney Transplantation: What Progress in 30 Years of History?

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Abstract

Completely unknown before the 90s and exceptional up to the 2000s, BK virus nephropathy (BKvN), usually known as polyomavirus-associated nephropathy, has emerged as a significant and severe viral complication in kidney transplantation (KT). More than twenty years after Gardner's discovery of BKv in 1971, Purighalla described, in 1995, the first case of BKvN. Four years later in 1999, Nickeleit et al. published a first series of five cases of BKvN and made very precious and pertinent contributions to understanding this new entity. It has been well established that in post-KT, 30 to 50% of kidney transplant recipients are positive for BK viruria, of whom approximately one-third will develop BK viremia and, without intervention, could progress in 1 to 10% of cases to BKvN, leading to kidney graft failure in more than half of the cases. For now, there is no preventive antiviral treatment for BKvN; only a strategy of rapid, efficient screening allows for the preservation of renal graft function. The only effective and sure treatment measure is to reduce the intensity of total immunosuppression, including immunosuppressive drugs and corticosteroids. Based on the current data, this review

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describes the physiopathology, diagnosis, and management of BKvN in adult KTRs. It presents the results of the fifty most important studies published during the last two decades.

Keywords
BK virus; nephropathy; kidney transplant; diagnosis; prognosis; graft failure

1. Introduction

Completely unknown before the 90s, exceptional until the 2000s, BK virus (BKv) infection, particularly BKv-associated nephropathy (BKvN), has emerged as a major and severe viral complication in kidney transplantation (KT). Despite much progress these last years in physiopathology, risk factors, diagnostic tools, screening, prevention, and treatment of BKvN, its incidence and the associated loss of kidney grafts are strongly present with minimal therapeutic options. BK virus (BKv) is an abbreviation for the name of the kidney transplant patient who presents a urethral stenosis. Gardner first identified the virus in the urine in 1971 [1]. More than twenty years later, in 1995, Purighalla described the first case of nephropathy associated with BKv in KT [2]. Four years later, in 1999, Nickeleit et al. published the first series of five cases of BKvN and made precious and pertinent contributions to understanding this new emerging entity [3]. Since then, this entity has been reported by many authors as a crucial viral complication that leads to graft loss in kidney transplant recipients (KTRs) [4-6]. According to some recent studies, BKv infection emerges as the most relevant viral complication, ahead of the other viruses, particularly cytomegalovirus and the Epstein Bar virus, with the highest prevalence, highest viral load, and lowest clearing rates [7].

Since these first descriptions, it has actually been well established that 30 to 50% of KTRs are positive for BK viruria, of whom approximately one-third will develop BK viremia and, without intervention, could progress in 1 to 10% of cases to PyVAN, leading to kidney graft failure in more than half of the cases [8, 9]. The prevalence of BKvN remains higher and varies according to inclusion criteria for patients and the tools used for diagnosis (biological as opposed to histological), from 1.5% to 30% [10-12]. The highest prevalence levels of BKvN have been mainly reported by authors who included in their series only KTRs who had benefited from a graft biopsy, indicating the positivity of BKv viruria and/or viremia [13, 14]. However, without a histological diagnosis, the prevalence decreases and does not exceed 10% [10, 15]. This considerable variability of BKvN prevalence in different KT centers likely reflects differences in the programs regarding the immunosuppression protocols, the biopsy policies for surveillance and indication, and the global approach toward diagnosing BKvN. It seems very relevant to note that the introduction of tacrolimus in the 1990s entirely coincides with the emergence of BKvN, indicating the significant role of all tacrolimus-based immunosuppressive regimens in the occurrence of this complication, even if other factors also play an important role and increase the risk of BKvN, such as male gender and lymphocyte depleting induction [15, 16]. Indeed, tacrolimus is implicated, but the association of tacrolimus-mycophenolate is even more strongly associated with the occurrence of BKvN. Viral infections are generally Mycophenolate-dependent, and all therapeutic measures are based on the reduction of Mycophenolate first. In 2020, the risk of BKvN remains high due to the intense use of tacrolimus and Mycophenolate association; more than 90% of current immunosuppressive regimens in a KT

setting include combining these two immunosuppressive agents. In addition, the increasing performance of incompatible human leucocyte antigen (HLA) and ABO kidney transplantation requiring more powerful immunosuppression, both induction and maintenance, contributes to enhancing the incidence of BKvN [17, 18]. This review aims to determine an accurate physiopathological and diagnosis approach to BKvN in adult KTRs.

2. Physiopathology of BKvN

BKv infection is acquired early in childhood; 60% to 80% of adults have antibodies to this virus, and most infections are subclinical and lead to viral latency within kidney tissue [19]. Asymptomatic viruria occurs in 0.3% of non-immunosuppressed patients, 3% of pregnant women, 10% to 45% of KTRs, and 50% of bone marrow transplant recipients [19]. According to the Organ Procurement Transplant Network National Registry in the United States (OPTN), the cumulative Kaplan-Meier incidence of BKvN keeps rising over time, from 0.70% at 6 months to 2.18% at 1 year, 3.45% at 2 years, and 6.6% at 5 years post-KT [20]. In this large study, including 48,292 primary and solitary kidney transplants from January 2003 to December 2006, the risk of BKvN was higher with specific immunosuppressive regimens, including rabbit antithymocyte globulin, tacrolimus, mycophenolate or combination of these molecules. A close examination of the first case published in 1995 by Purighalla brings out pertinent elements [2]. This concerned a young man 34 years of age, having had a kidney transplant to replace a polycystic kidney. He had received tacrolimus-based immunosuppression with prednisone without antilymphocyte induction therapy. He also presented several episodes of acute rejection for which he received corticoid bolus. Still, the article does not mention the frequency and dosage, although there is a clear context of solid immunosuppression. A graft biopsy was performed thirty-eight weeks post KT due to another episode of allograft dysfunction, and the changes were consistent with rejection and BKv inclusions. Several kidney biopsies were taken during plasma creatinine elevations (41, 44, and 45 weeks) and showed a combination of rejection and viral infection. Attempts to lower the immunosuppression and eradicate viral infection resulted in graft loss 56 weeks post-KT in this case. Four essential points can be deduced from this case, which we find again later in published series that are larger and richer in clinical, biological, and histological data. First, BKvN occurs early on during the first year post-KT. Second, BKvN occurs in intense immunosuppression, including induction and maintenance of immunosuppressive regimens. Third, BKvN is often preceded and/or associated with acute rejection episodes. Fourth, BKvN can lead to the total loss of the kidney graft. What is the mode of action and what are the specific features of BKv? The human polyomaviruses are ubiquitous, small (40-45 nm), circular, nonenveloped icosahedral capsids containing double-stranded DNA genomes of approximately 5,000 base pairs [21]. Two polyoma-viruses are known to infect humans normally, JC virus (JCV) and BK virus (BKv), both discovered in 1971. However, the classification of SV40 as a human polyomavirus is still widely debated. Figure 1 shows the most important human polyomaviruses identified and their main clinical presentations.

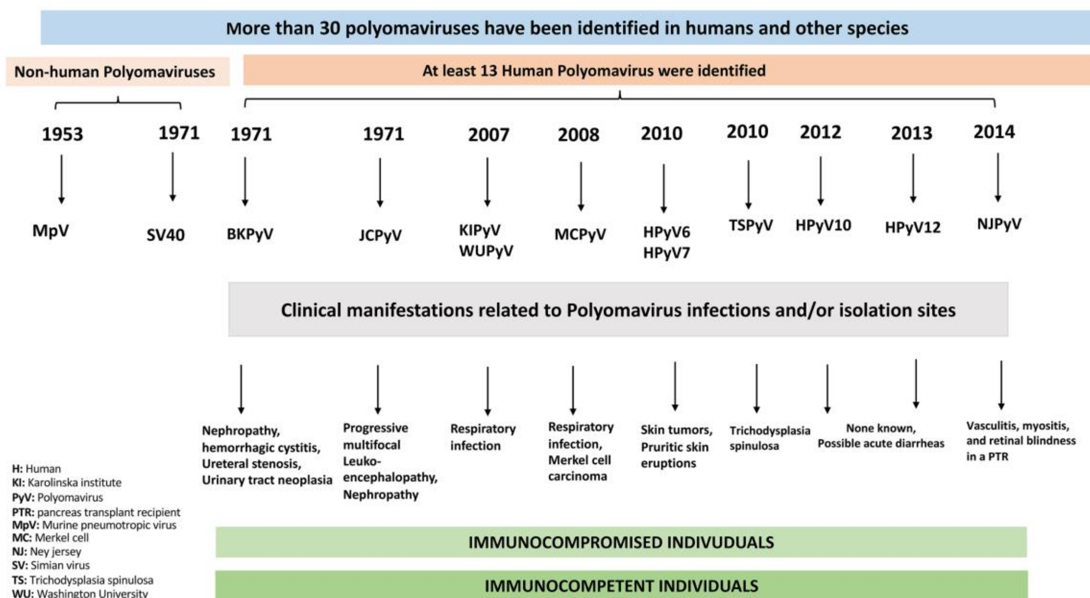

Figure 1 The most important human polyomaviruses identified and their main clinical presentations.

It should be noted that BKv mainly affects the urinary tract and induces BKvN in the context of KT, as well as hemorrhagic cystitis in the context of stem cell transplant. Urethral stenosis and hydronephrosis are also found. However, it is rare to find extra-urinary complications such as pulmonary, hepatic, neurologic, and retinal impairment, and oncogenic risk remains controversial [22]. BKvN is typically found in renal allografts and rarely in native kidneys [23]. After primary infection, usually asymptomatic and occurring in childhood, the polyomaviruses establish latency in tubular epithelial cells of the kidney without untoward effects until states of immunosuppression permit transition from latent to active phases. The relatively slow progression of viruria to viremia to nephropathy provides the opportunity to detect BK virus infection [8]. The appearance of BK viruria constitutes a first alarm signal that must trigger a rapid and systematic search for viremia. A positive BK viremia result is a second alarm signal that must trigger a rapid and systematic search for BKvN. In KTRs, the target renal cells of the cytopathogenic effect of BKv are the epithelial cells (tubular cells and epithelial cells of Bowman's capsule). The BKv initially replicates in the distal tubular epithelial cells and mainly in the medulla, leading to necrosis and local damage and inflammation initiation. The first step of BKvN is BKv reactivation in tubular cells, resulting in the accumulation of virions in the cell nucleus (intranuclear inclusions). The infection of the tubular cell progresses towards its necrosis, detachment, and then elimination in the urine corresponding to the decoy cells, which are usually sought in the urine of all KTRs. The second step occurs many weeks later, especially in the presence of a considerable viral load and in the context of deep immunodepression, when the infection extends to the blood, leading to viremia.

The exposition of renal tubular cells to viral RNA directly stimulates the viral receptors of the innate immune system, including TLR3 (Toll-Like-Receptors 3) and RIG-I (Retinoic Acid-Inductible gene I). After this bond, the receptors activate transcription factors such as NF-κB and induce antiviral and proinflammatory responses by producing type I IFNs or proinflammatory cytokines such as IL-6, IL-12, or TNFα [24]. TNFα is one of the most important inflammatory factors and mediates its biological activity (proinflammatory and immunosuppressive effects) by binding to one

of its receptors, TNFR1 or TNFR2, and the TNFα/TNFR complex is known to be an important component of the immune system involved in the control of viral infections [25]. These receptors are widely present in the glomeruli, peritubular capillaries, and tubular epithelial cells of the kidneys. The BK virus genotype could also play an important role in the pathophysiology of kidney damage. In Furmaga's study, BK virus infection with genotype I tended to adversely affect kidney function more than genotype IV, which was associated with anemia [26].

At an advanced stage and lacking therapeutic intervention, the histological lesions, initially focal and predominantly distal and medullary, will diffuse and spread to the proximal and cortical segments. The inflammatory lesions will develop into interstitial fibrosis and tubular atrophy. The passage from one stage to another requires several weeks, which shows the importance of early detection and prompt, adequate treatment to avoid the rapid progression of BKvN towards severe forms with poor prognosis. Thus, the sequence of the progression is as follows: the onset of BK viruria typically occurs during the first weeks post-transplantation, followed by BK viremia about 2 to 6 weeks later. Viruria and viremia almost always precede BKvN, which in three-quarters of cases appears during the first year post-transplantation, with a median onset at 12 weeks after viruria, i.e. 2 to 6 weeks after viremia [8]. Figure 2 shows the chronology of the evolution of BK virus infection in kidney transplantation recipients.

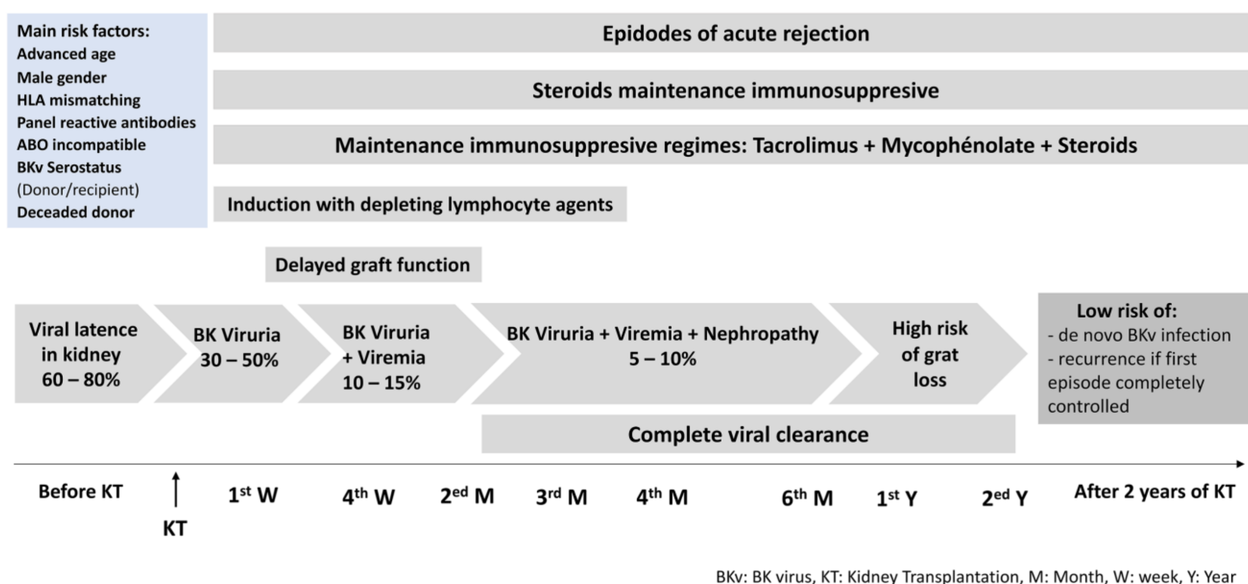

Figure 2 The chronology of the evolution of BK virus infection in kidney transplantation recipients.

3. Diagnosis

BKvN is a tubule-interstitial nephropathy and clinical information is therefore sparse, usually limited to an isolated increase of creatinine, without other associated clinical and/or laboratory signs. The diagnosis of BKv infection relies on the search results for viral replication in urine and blood. In contrast, diagnosing BKvN relies on histological criteria of viral replication in kidney tissue. Kidney biopsy has an important place in this context to confirm the BKvN diagnosis and search for acute rejection and/or nephrotoxicity to anticalcineurins associated with BKvN. It is important to point out that two forms of BKvN are usually distinguished in the literature: the first form is the

“definitive” BKvN that is proven at graft biopsy, and the second is the “presumptive” BKvN that is strongly suspected with a positive BK viremia, but without histological criteria. There are some reasons for the absence of histological criteria. On the one hand, there are false negative results from the graft biopsies performed, observed in 10 to 30% of cases, because the viral lesions are focal and predominately in the medulla [8, 9]. On the other hand, allograft biopsies may not be performed due to a medical contraindication or because the transplantation medical team does not routinely perform allograft biopsy if BKvN is suspected, incredibly when renal function is preserved unless they suspect an association with acute rejection.

In October 2003, an international panel of transplant physicians, nephrologists, pathologists, virologists and infectious disease specialists convened in Basel, Switzerland, to analyze existing information regarding BKvN in KT [27]. This meeting established the histological classification and strongly recommended allograft biopsy for BKvN diagnosis. In 2009, The Kidney Disease Improving Global Outcomes (KDIGO) guidelines did not recommend allograft biopsy for BKvN [28]. In 2018, the American Society of Transplantation Infectious Diseases Community of Practice guidelines suggested that in KTRs without increased risk of acute rejection and baseline renal function, renal allograft biopsy was not required before reducing immunosuppression [29]. In these last guidelines, allograft biopsy should primarily be considered for patients with renal allograft function decreased from baseline or having markers indicating an increased immunological risk such as highly sensitized status with panel reactive antibodies, presence of a donor-specific antibody, blood group incompatibility, re-transplantation, or a history of acute rejection.

In 2022, Consensus Definitions of BK Polyomavirus Nephropathy in Renal Transplant Recipients for Clinical Trials was published, including the definitions of the different parameters associated with BK virus infection post-kidney transplantation [30]. In this paper, proven BKvN requires demonstration of active BKv replication within kidney tissue by at least one of the following methods: immunohistochemistry staining reaction for SV40-T antigen or in situ hybridization and demonstration of BKv DNAemia using a previously well-validated assay. In clinical practice, kidney allograft biopsy is considered the gold standard for diagnosing BKvN. Moreover, biopsy has utility because staging classifications for BKvN exist, and more significant interstitial fibrosis, tubular atrophy and inflammation on the biopsy index are correlated with worse outcomes, including viral clearance and graft loss. In this context, allograft biopsies remain essential to determine the class of BKvN given establishing a renal prognosis and acting in consequence. The specific diagnosis of BKvN should be sought by demonstrating polyomavirus cytopathic changes in kidney allograft tissue and be confirmed by an ancillary technique such as immunohistochemistry for BKv proteins or by in situ-hybridization for BKV nucleic acids. These cytopathic viral changes are often associated with epithelial cell necrosis, acute tubular injury, varying degrees of inflammatory cell infiltrates, tubular atrophy, and fibrosis. A minimum of 2 biopsy cores should be taken, preferentially containing medullary tissues due to the natural localization of BKvN. Negative initial kidney allograft biopsy and sustained BK viremia corresponds to “presumptive BKvN” which is frequent, with prevalence from 20% to 80% of all cases of BKvN [31, 32]. In this context, repeated kidney graft biopsies appear to be justified.

Several histological classifications of BKvN have been formulated since 2001. The first quite precise histological classification of BKvN was developed in 2003 by a group of experts (Hirsh et al.) and produced a rather interesting description of the central renal histological lesions characteristic of BKvN [27]. In 2009, Masutani et al. proposed a classification of BKvN that includes three stages,

modified from histologic patterns of BKvN reported by Drachenberg in 2004: stage A (early changes, without tubular epithelial cell necrosis), stage B (active nephropathy with virally induced tubular necrosis), and stage C (late sclerosing changes). In 2018, Nickeleit et al., in the Banff Working Group Classification of Definitive Polyomavirus Nephropathy framework, proposed adding a new Polyomavirus load level (pvl) score [33]. However, the current classifications are not used by all transplantation teams; some teams use the BKvN classification with only one class in B, and others use the classification with the three sub-classes of B (B1, B2, and B3). Class B generally makes up more than 50% of all histological classes of BKvN and sometimes reaches more than 80% in specific series [33]. It is noteworthy that class B1 may be confused with class A, and class B3 may be confused with class C, resulting in errors in recognition of the actual class. All of this points to the interest of a renewed discussion about the pertinence of the three sub-classes of class B. Diagnosing BKvN with certainty depends on the histological study of the renal graft biopsy, which is only performed under criteria of solid suspicion, including urinary and/or plasma signs of viral replication with or without alteration of renal function.

Kidney graft biopsy is never performed without biological evidence of BK virus infection. There are some biological blood and urine parameters that can diagnose BKv infection. All learned societies have identified and validated three biological parameters of viral replication to standardize the diagnostic approach and screening for BKvN [28]. There are two urinary parameters: decoy cells (>10 cells per cytospin) and urine BKv DNA quantitative PCR (>10^7 copies/mL); the other is a blood parameter, blood/plasma BKv DNA quantitative PCR (>10^4 copies/mL). The lack of standardization of quantitative PCR between the different Transplant Centers, particularly for blood analysis values, is a significant limitation to the formation of an ideal consensus. Urine testing has a high negative predictive value and also a window period of 12 weeks where urine BK levels may be rising prior to the occurrence of BK viremia.

The search for “decoy cells” by Papanicolaou coloration is an effective means of early qualitative identification, but the anatomical pathologist needs to be trained in this cytologic interpretation. “Decoy cells” correspond to tubular epithelial cells infected with BKv, which are then shed in the urine. They have large, basophilic nuclei with viral inclusions and appear similar to those in uroepithelial cancer. Decoy cells' positive and negative predictive values for identifying BKvN are 29% and 100%, and their sensitivity and specificity are 25% and 84%, respectively [8]. The advantage of this urinary tool is that is simple to set up, easy to generalize, non-invasive, inexpensive, and has a negative predictive value of 100%. Papanicolaou staining remains widely used to screen decoy cells, but other stains can be used to diagnose decoy cells, such as Sternheimer-Malbin staining and Wright-Giemsa staining [34]. Thus, it is a perfect screening tool for BKv infection, and a PCR plasma assay for BKv must follow up at the slightest suspicion of BKvN. Another indication of the presence of the virus in the urine is the detection of Haufen. Indeed, Haufen are icosahedral aggregates of a minimum of six polyomavirus particles and Tamm-Horsfall protein that can be detected in the urine of KTRs with BKvN using negative-staining electron microscopy. The positive and negative predictive values of Haufen for identifying BKvN are 97% and 100%, respectively, and their sensitivity and specificity are 100% and 78%. Despite its substantial positive predictive value and strong sensitivity, this test remains little used. It is not recommended because of its extremely high cost and the need for an electronic microscope.

Another urinary parameter is being evaluated, CXC-ligand 10 (CXCL10), a chemokine that attracts and activates immune cells with a cytokine profile of T-helper cells Type 1. A valuable role for CXCL10

in graft dysfunction has not been demonstrated, but it appears to be an exciting biomarker for assessing BKv replication [35]. It is Currently not routinely practiced but remains exciting and will probably constitute a good urine test for screening for BKv infection in the years to come. Indeed, Weseslindtner L et al. demonstrated in their retrospective study that CXCL10 in urine and blood already rises during early BKvN replication gradually increases in proportion with the extent of viral replication, and correlates with the progression towards BKvN [36]. Haller and al. confirmed the findings from Weseslindtner and reported three major findings in their study: urine CXCL10 levels started to rise with the presence of viruria, urine CXCL10 levels closely followed the course BKvN DNAemia and low urine CXCL10 levels allow to rule out relevant BKv viruria and BKv DNAemia with high certainty [37]. When et al., in their recent study, developed a novel algorithm based on monitoring of plasma Graft-derived cell-free DNA (GcfDNA) levels after a kidney transplant that promising results in identifying and predicting BKvN [38]. As with graft rejection, graft injury caused by BKvN may also increase GcfDNA levels in the urine or blood. GcfDNA originates from algorithmrafts and is considered a potential noninvasive marker for evaluating graft injury.

It should be noted that in KTRs with proven BKvN and absence of BK virus - DNAemia in blood, urine, and graft tissue, JC polyomavirus-associated nephropathy should be considered, and specific Quantitative Nucleic Acid Testing (QNAT) be sought on urine, blood, and allograft tissue. JC virus nephropathy is much lower than BK BKvN in post-kidney transplantation but not neglectable (<10% of all cases). Drachenberg C et al. found six cases (5.8%) of JC nephropathy in kidney transplant recipients, among 103 included in the study with positive decoy cells [39]. Otherwise, the presence of decoy cells points simultaneously towards the presence of BK and/or JC polyomavirus. In contrast, the selective search of BK viruria (BKv DNA quantitative PCR) does not exclude the infection by the JC virus. Whatever the presentation with a strong suspicion of JC nephropathy, the kidney graft biopsy must make or exclude the diagnosis.

Gras et al., studied the kinetics of BKv replication in plasma and kidney in 32 kidney transplants with biopsy-proven BKvN [40]. They found that the genotype identified early post-transplant in the kidney is different compared to the genotype identified at the time of BKvN, suggesting that the donor strain did not only contribute to the pathogenesis of these cases. They also noted a robust BKv-VP1 NAb (BK virus-neutralizing antibodies titers) response. Siripoon et al. found that nonspecific and VP1-specific natural killer cells before KT and increasing numbers of these cells after KT were associated with a high risk of BKv viruria and presumptive BKvN [41].

4. Screening

Laboratory tests for BKv replication are screening tests carried out systematically on all KTRs. All the national and international learned societies recommend these tests, with only the rhythm and nature of the tests sometimes differing from one society to another. KDIGO, in 2009, recommended screening all KTRs for BKv with plasma QNAT at least monthly for the first 3-6 months after transplantation, then every 3 months until the end of the first post-transplant year, whenever there is an unexplained rise in serum creatinine, and after treatment for acute rejection [28]. The guidelines of The American Society of Transplantation Infectious Disease Community of Practice, published in 2019, recommended that all KTRs be screened for BKvN-DNAemia by QNAT to identify patients for preemptive treatment for PyVAN. This screening for BKvN-DNAemia by QNAT should be performed monthly until month 9, then every 3 months until 2 years post-transplant. KTRs should

be tested for BKvN-DNAemia by QNAT when undergoing renal allograft biopsy for surveillance or for cause/indication to inform histopathology studies [29]. In these last recommendations, the authors added that BKvN-DNAemia should be confirmed within 3 weeks to be sustained as plasma BKv loads >3 $\log_{10}$ c/mL (probable BKvN) or to be increasing to plasma BK virus loads of >4 $\log_{10}$ c/mL (presumptive BKvN). The threshold of 4 $\log_{10}$ of plasma BKv load is a positivity threshold retained by all learned societies for "presumptive BKvN" and should lead to lowering immunosuppression without acute rejection. In contrast, the threshold of 3 $\log_{10}$ of plasma BKv load is an alarm signal that must trigger a second test of plasma virus load two weeks later because viral replication can be rapid and significant, and the viral load may evolve from 3 $\log_{10}$ to 4 $\log_{10}$ in two weeks. Besides the learned society recommendations, BKvN screening algorithms are regularly published by different experts in the field [42]. Table 1 reports the summary of BK virus screening methods, their target definition values and their predictive values.

Table 1 BK virus screening methods: Target definition values and predictive values.

Screening method (Urinary and plasma)	**Urinary criteria**	**Positive predictive value (%)**	**Negative predictive value (%)**
Urinary decoy cells	>10 cells per cytospin	+	++++
Urinary BK virus DNA quantitative PCR	>1 × 10^7 copies/mL	++	++++
Urinary BK virus loads	>4 $\log_{10}$ copies/mL		++++
Urinary Houffen (agregats of polyomarivus particules and Tamm horsfall protein)	agregates of a minimum of six polyomaviruses on electron microscope	+++	++++
Plasma BK virus DNA quantitative PCR	>1 × 10^4 copies/mL	++	++++
Plasma BK virus loads	>7 $\log_{10}$ copies/mL	++	++++

+ <30%, ++ 30-70%, +++ >70-99%, ++++ 100%.

Moreover, the expertise of each transplantation team and the means available may give rise to different approaches to screening for BKv infection and BKvN, which generally respect the broad lines developed by international recommendations. For example, according to local resources (human competences and technical means), some transplantation teams use decoy cells as their first-line screening method for BKv infection. In contrast, others use the plasma PCR assay of the BKv immediately. What is most important is to master the available means to ensure early and rapid screening of BK virus infection and, consequently, that of BKvN.

5. Risk Factors

The main irrevocable risk factor is the intensity of overall immunosuppression during the first months post-transplant. This includes induction treatment, maintenance treatment, and treatment for possible acute rejection episodes before BKvN diagnosis. Concerning induction immunosuppression treatment, lymphocyte-depleting antibodies (LDA) play a more important role compared to other induction treatments such as basiliximab or daclizumb or the absence of induction [20]. In numerous series, patients presenting a BKvN proven at biopsy received LDA as induction in more than 50% of cases [43]. Jahadi et al. and Huraut et al. reported their use in 100%

of their patients with BKvN [10, 44]. However, other studies report a very low use of LDA in less than 10% of all cases, even no use [11]. The involvement of LDA in the genesis of BKvN remains controversial. In contrast, the maintenance immunosuppression regime based on tacrolimus and mycophenolate mofetil (MMF) is closely linked to the genesis of BKvN since more than 95% of patients presenting BKvN receive treatment based on calcineurin inhibitors (CNIs) and MMF, and more than 90% of patients on CNIs receive tacrolimus [33]. The intensity of this immunosuppression is the major risk factor and the increase of tacrolimus T0 (>10 ng/ml) and the Area Under the Curve (AUC) of the MMF (>60 h.mg/L) during the first three months post-transplant is strongly correlated with the occurrence of BKvN [20].

In the first series published in the literature by Nickeleit in 1999, concerning five cases of BKvN, the authors pointed out that there had been no case of BKvN among the 616 renal transplants performed between 1985 and 1995, an era preceding the introduction of tacrolimus [3]. In this series, the five patients had presented at least one acute rejection episode before the diagnosis of BKvN treated by corticoid bolus. They had all undergone a switch from cyclosporine to a high dose of tacrolimus without MMF. This highlights the major role of high-dose tacrolimus in the reactivation, rapid and intense viral replication and BKvN, and is a call for adjusting the T0 prograff targets downwards, particularly in patients at high risk for BKvN. In a current study entitled "An open-label, randomized trial indicates that everolimus with tacrolimus or cyclosporine is comparable to standard immunosuppression in de novo kidney transplant patients" published in 2019, the authors found that there were significantly fewer BKv infections in the Everolimus/Tacrolimus and Everolimus/Cyclosporine groups versus Mycophenolic acid/Tacrolimus ($p = 0.001$). This finding was assessed from urine or blood samples based on local reverse transcriptase PCR analysis ($>10^3$ copies/mL) and clinical assessments and histology where available [45]. BKv infection with organ involvement was reported in three Everolimus/Tacrolimus patients, one Everolimus/Cyclosporine patient and six Mycophenolic acid/Tacrolimus patients. Might the solution to reduce the prevalence be a return to cyclosporine? Before the BKvN diagnosis, patients with BKvN often present episodes of acute rejection treated with corticiotherapy and/or LDA. This contributes to a context of deeper immunodepression and is favorable to the rapid and robust reactivation of the BKv. The acute rejection prior to BKvN may be found in up to 50% of patients and may be either a cellular or humoral acute rejection [46, 47].

Male gender is also found in all the studies and up to 85% of patients with BKvN are male [48, 49]. The deceased donor is also found in the majority of studies and may contribute to BKvN through a high degree of mismatching, the phenomenon of ischemia-reperfusion, delayed renal function and recourse to more intensive immunosuppression. The prevalence of deceased donors varies from 20 to 100%, according to the studies [48, 50]. Advanced age is also a known risk factor. However, the median age reported by the majority of studies, including only adult KTRs, is not very advanced, between 28 and 56 years, with 80% of the reported median ages falling between 45 and 55 years [44]. In the large cohort of Nickeleit et al., including 192 patients with BKvN, the median age was 53 years [33]. Only Solis et al. found a median age higher than 60 years (62.8 years) in their series of 13 patients with BKvN [46].

In pre-kidney transplantation and due to a lack of scientific evidence, anti-BK virus antibody serology is not performed in the donor and the recipient, unlike other viruses (CMV, EBV…) for which serology is systematically performed. Salakova et al., in their study, noted that the BK virus-specific antibodies were identified as a predictive factor for BK-DNAemia and BKvN [51]. Bae et al. noted

that the combination of high donor BKv-IgG, low recipient BKv-IgG, and low total BKv-ELISPOT results predicted BK viremia after KT [52]. Further studies are needed to define the anti-BKv-IgG cut-off levels to predict post-kidney-transplant BKv infection. Gras et al. reported that lymphopenia below 500/mm and corticosteroid maintenance therapy above 7.5 mg/day have been identified as significant risk factors in multivariate analysis for BKvN [12]. Table 2 reports the main risk factors associated with BKvN in adults post KT.

Table 2 Main risk factors associated with BKvN in adult kidney transplantation.

Risk-factors of BKvN	
Donor-related risk factors	**Recipient-related risk factors**

HLA-incompatibility
ABO-incompatibility
Deceased donation vs living donors
Female gender
African American ethnicity
Older donor age
High BK virus-specific antibody titers
HLA Cw7
Ischemia-reperfusion injury
	HLA-incompatibility (Degree of HLA mismatching):
	ABO-incompatibility
	Deceased donation vs living donors
	Male gender
	Non-African-American ethnicity (White ethnicity)
	Older recipient age
	History of hemodialysis as opposed to peritoneal dialysis
	Diabetes mellitus
	Low or absent BK virus -specific antibody titers
	Low or absent BK virus-specific IgA or T-cell activity
	Anti-neutrophil cytoplasmic antibodies
	1,25-Dihydroxyvitamin-D3 deficiency
	Lymphopenia
	Ureteral stents
	Delayed graft function
	Cold ischemia time
	Cytomegalovirus infection
	Degree of overall immunosuppression (IS):
	  Treatment of acute rejection
	  Cumulative steroid exposure
	  Lymphocyte-depleting antibodies
	  Tacrolimus combination IS
	  Tacrolimus and/or MMF based maintenance IS
	  Levels of tacrolimus
	  Metabolism of tacrolimus

6. Prognosis and Management

The goal of BKvN treatment in the earlier stages (A and B) is to limit viral replication and prevent disease progression to late stage (C). For the advanced stages (B and C), the main goal is to completely control the infection and avoid the loss of the graft. In 2018, Nickeleit et al. studied a large multicenter cohort (American and European) of BKvN cases proven at allograft biopsy and analyzed the renal prognosis according to the BKvN stages [33]. In this large cohort, the working group collected data on 192 patients with biopsy-proven definitive BKvN transplanted between 1996-2008 (50% between 2006 and 2008). The median age of recipients was 53 years. 74% were men, 49% were white, and 64% of organs were from deceased donors. BKvN was diagnosed in the index biopsy between 4 and 582 weeks post-transplantation (median of 28 weeks). During the time before diagnosis of BKvN, 58% of patients had undergone renal biopsy, with a diagnosis of acute allograft rejection in 24%. According to other studies, graft loss with return to dialysis varies from 0% to 47% [53]. Table 3 reports renal outcomes according to this large multicenter cohort study published by Nickeleit et al. In the two series of Chenet et al. and Menter et al., graft loss was not observed in any cases among the 24 and 35 patients with BKvN enrolled, respectively in their studies, but these cohorts included only A and B classes without class C [13, 32]. The plasma creatinine level is relatively low in the series where the graft loss rate is 0%, compared to the series where the graft loss rate is high, exceeding 20%. In the series of Shaub et al., graft loss was 0% even if the median plasma creatinine level was 1.5 mg/dL [53]. The highest rates of graft loss exceeding 30% were observed in series, including at least 10% of class C. In the series of Huang et al. (including 48 cases of BKvN), graft loss was seen in 39.5%, and 12% of PyVAN cases were class C; the plasma creatinine level at the time of BKvN diagnosis was high, at 2.7 mg/dL [16]. In a series of Gras et al., 34% of the 64 patients who had BKvN returned to dialysis vs 5% of the 64 control patients without BKvN ($p < 0.001$) [12].

Table 3 Kidney outcomes according to a sizeable multicentric cohort of patients who developed BKvN proven at allograft biopsy after kidney transplantation.

BK virus associated Nephropathy	**All classes of BKvN**	**BKvN Class A**	**BKvN Class B**	**BKvN Class C**	**p-value**
At the start of study	N = 192	-	-	-	-
After reinterpretation of kidney anatomical pathology	N = 178	N = 44	N = 112	N = 22	-
Serum creatinine 4 months before BKvN	-	1.4 mg/dL	1.5 mg/dL	1.8 mg/dL	0.13
Peak serum creatinine at index biopsy	-	1.8 mg/dL	2.1 mg/dL	2.7 mg/dL	<0.001
Change in serum creatinine baseline to peak	-	0.3 mg/dL	0.6 mg/dL	0.8 mg/dL	<0.001
Time diagnostic to BKvN	-	18 weeks	30 weeks	54 weeks	<0.001
Median increase of serum creatinine during the 24 months of followup	-	0.4 mg/dL	1.0 mg/dL	4.8 mg/dL	<0.001

Resolution of BKvN	N = 159 117/159 (74%)	75%	78%	50%	0.17
Median time to resolution of BKvN	N = 159 17 (12-44)	12 weeks	24 weeks	14 weeks	0.26
Viral clearance of plasma PCR	-	20/29 (69%)	54/73 (74%)	5/14 (36%)	0.15
Time to viral clearance	-	12 weeks	24 weeks	48 weeks	0.23
Graft loss at 24 months (return to dialysis, retransplantation, and/or serum creatinine ≥7.0 mg/dL)	N = 189 56/189 (30%)	16%	31%	50%	0.004
Acute rejection or other severe complications	-	7%	25%	38%	0.01

Retransplantation is not contraindicated after graft loss by BKvN. Transplant nephrectomy is not required either; however, BK viral load (in plasma and urine) should be undetectable to minimize the risk of recurrence [54]. An analysis of the American registry (OPTN) data identified 823 kidney recipients who experienced graft loss due to BKvN of which 15% (126 patients) were retransplanted, with a median wait time from the failure of the prior graft to retransplant of 314 days [55]. A more recent study of the same registry confirms the previous results published in 2010 and does not show a high risk of graft loss in patients retransplanted after graft loss by BKvN [56]. Retransplants received similar induction and maintenance immunosuppression as first-time recipients; 1- and 3-year graft survival rates in retransplanted recipients (68 among 121) were 99% and 94%, respectively, with only one graft loss due to recurrent BK nephropathy.

Acute rejection is a severe complication often concomitant to BKvN or appearing after the reduction of immunosuppression. Any allograft biopsy performed because of suspicion of BKvN must systematically search for histological signs of associated cellular or humoral acute rejection. The diagnosis is sometimes difficult, especially in the early stages of BKvN, and acute rejection is concomitant to BKvN in 10 to 40% of cases [14, 50]. In the series of Gras et al., 19% of the 64 patients who had BKvN developed acute rejection vs 3% of the 64 control patients without BKvN ($p = 0.003$) [12]. The only effective and sure treatment measure is to reduce the intensity of total immunosuppression, including immunosuppressive drugs and corticosteroids. This can be done in two ways: by reducing the doses of already prescribed treatments or switching to other molecules with lesser immunosuppressive power. The Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice, published in 2019, recommend reducing maintenance immunosuppression as the primary treatment of sustained BKv-DNAemia, probable BKvN, presumptive BKvN, or proven BKvN in KTRs without concurrent acute rejection [29]. Concerning the strategy for dose reduction of already prescribed immunosuppressive treatments, these guidelines recommend that tacrolimus trough levels be commonly targeted to <6 ng/mL, cyclosporine trough levels to <150 ng/mL, and mycophenolate mofetil/mycophenolicacid daily dose equivalents be less than or equal to half the daily maintenance dose (1 gramme per day). In severe forms, and after the failure of the initial reduction in immunosuppression, a larger drop below these recommended targets (tacrolimus target <4 ng/mL) and mycophenolate mofetil/mycophenolicacid

daily dose equivalents be less than half the daily maintenance dose (i.e. mycophenolate mofetil 500 (or even 250) mg twice daily) are necessary to obtain viral clearance. It should be noted that immunological monitoring in search of donor specific antigen (DSA) antibodies should be very close and rigorous in this context and any worsening of renal function must make one think of rejection and carry out a biopsy accordingly. Concerning the switch strategy, the guidelines recommend switching from tacrolimus to low-dose cyclosporin, or switching from Tacrolimus/Cyclosporin to sirolimus, or switching from mycophenolates to low-dose sirolimus, or from mycophenolates to leflunomide. The switch from one molecule to another remains little practiced in reality because the change can favor the appearance of a rejection episode or a serious side effect. The best option is the concomitant reduction of the two immunosuppressive molecules (antiproliferative and anticalcineurin agents), which the patient previously tolerated well. In case of failure of this reduction and/or switch strategies, even well conducted, in patients with sustained BKv-DNAemia, probable BKvN, presumptive BKvN, or proven BKvN, the use of adjunctive therapies may be considered.

However, adjuvant therapies are minimal and can be summed up as a few molecules: leflunomide, cidofovir, ciprofloxacin, and intravenous immunoglobulins (IVIG), initially promising but with results that have proved disappointing. In their meta-analysis, Johnston et al. did not find an allograft survival benefit with adding cidofovir or leflunomide to immunosuppression reduction [57]. Immunoglobulins, very effective in other types of post-KT viral infections such as parvovirus infection, have not shown encouraging results for BKv and their use is not recommended [58]. Attempts to prevent BK virus infection with ciprofloxacin showed no interest and was quickly abandoned [59]. At this time, the use of cidofovir or leflunomide as adjuvant therapy for BKvN is not recommended. Furthermore, recommendations are clear concerning the association of BKvN with acute rejection. The risk of immunosuppression reduction is the development of acute rejection, underlining the importance of monitoring, particularly immunologic, for early detection of any rejection episode. Baek et al. studied 79 patients with immunosuppression reduction for presumptive BKvN and found that 21.5% of them experienced acute rejection at 31.4 ± 22.2 months (range, 1-74 months; median, 34 months) after immunosuppression reduction [60]. By comparing the combination of intravenous immunoglobulin and leflunomide versus IVIG to treat BKvN after kidney transplant, the authors found that the addition of leflunomide to the IVIG treatment seems to have a better effect in reducing BK viral load after three months of treatment [61]. In KTRs with sustained BKvN-DNAemia and biopsy-proven acute rejection, as evidenced by intimal arteritis or positive C4d stain (with or without proven BKvN), anti-rejection therapy should be given first, followed by reducing immunosuppression as a second step. Viral clearance and resolution of the BKvN require several weeks, an average of 12 weeks for stage A, and up to 24 weeks for classes B et C [33]. In a retrospective French study, the authors demonstrated that IVIG administration (44 high-risk treated patients vs 41 high-risk untreated patients) can prevent BK virus viremia and BKvN in KTR with low BK virus-neutralizing antibodies titers [62]. A recent study by Sato et al. in Japan provided a therapeutic basis for the prophylactic and preemptive treatment of BKv infection with IVIG, possibly reducing the risk of BKv-related complications, such as BKvN [63]. Further studies are needed to establish a preventive approach using intravenous immunoglobulins.

7. Conclusion

Although uncommon, BKvN represents a significant threat to allograft survival. For now, there is no preventive or curative antiviral treatment for BKvN, and only rapid screening for viremia and the early stages of BKvN allow for the preservation of the renal graft. Renal biopsy is not performed systematically, regardless of whether BKvN is proven or presumptive. The therapeutic approach remains the same and is based on reducing immunosuppression under strict monitoring of viremia and detecting acute rejection. Identifying patients at high risk of BKvN seems worthwhile in establishing a more precise preventive strategy and a better-adapted immunosuppressive protocol. The challenges in general organ transplants and kidney transplantation are changing. From the immunological challenge of the 1980s to the infectious challenge of the 2000s. The emergence of these new viral infections as BK virus or parvovirus, often responsible for severe impairment, will lead in the following decades to redefine the targets of immunosuppressive drugs and to determine the serological profile of these viruses in pre-transplant assessment for high-risk patients. We need several randomized clinical trials to establish better the link between the targets of different immunosuppressive agents and the real infectious risk. While waiting for accurate and reliable data, only prevention through a good screening remains the most effective attitude.

Author Contributions

The author did all the research work of this study.

Competing Interests

The author declares that there are no conflicts of interest.

References

1. Gardner S, Field A, Coleman D, Hulme B. New human papovavirus (BK) isolated from urine after renal transplantation. Lancet. 1971; 297: 1253-1257.
2. 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: 671-673.
3. Nickeleit V, Hirsch HH, BINET IF, Gudat F, PRINCE O, Dalquen P, et al. Polyomavirus infection of renal allograft recipients: From latent infection to manifest disease. J Am Soc Nephrol. 1999; 10: 1080-1089.
4. Howell DN, Smith SR, Butterly DW, Klassen PS, Krigman HR, Burchette Jr JL, et al. Diagnosis and management of BK polyomavirus interstitial nephritis in renal transplant recipients. Transplantation. 1999; 68: 1279-1288.
5. Randhawa PS, Finkelstein S, Scantlebury V, Shapiro R, Vivas C, Jordan M, et al. Human polyoma virus-associated interstitial nephritis in the allograft kidney1. Transplantation. 1999; 67: 103-109.
6. Hirsch HH, Vincenti F, Friman S, Tuncer M, Citterio F, Wiecek A, et al. Polyomavirus BK replication in de novo kidney transplant patients receiving tacrolimus or cyclosporine: A prospective, randomized, multicenter study. Am J Transplant. 2013; 13: 136-145.

7. Blazquez-Navarro A, Dang-Heine C, Wittenbrink N, Bauer C, Wolk K, Sabat R, et al. BKV, CMV, and EBV interactions and their effect on graft function one year post-renal transplantation: Results from a large multi-centre study. EBioMedicine. 2018; 34: 113-121.
8. Hirsch HH, Knowles W, Dickenmann M, Passweg J, Klimkait T, Mihatsch MJ, et al. Prospective study of polyomavirus type BK replication and nephropathy in renal-transplant recipients. N Engl J Med. 2002; 347: 488-496.
9. Brennan DC, Agha I, Bohl DL, Schnitzler MA, Hardinger KL, Lockwood M, et al. Incidence of BK with tacrolimus versus cyclosporine and impact of preemptive immunosuppression reduction. Am J Transplant. 2005; 5: 582-594.
10. Hurault de Ligny B, Etienne I, Francois A, Toupance O, Buchler M, Touchard G, et al. Polyomavirus-induced acute tubulo-interstitial nephritis in renal allograft recipients. Transplant Proc. 2000; 32: 2760-2761.
11. Ma MK, Leung AY, Lo KY, Lio WI, Chan HW, Wong I, et al. Screening algorithm for BK virus-associated nephropathy using sequential testing of urinary cytology: A probabilistic model analysis. Am J Nephrol. 2016; 42: 410-417.
12. Gras J, Le Flécher A, Dupont A, Vérine J, Amara A, Delaugerre C, et al. Characteristics, risk factors and outcome of BKV nephropathy in kidney transplant recipients: A case-control study. BMC Infect Dis. 2023; 23: 74.
13. Chen XT, Li J, Deng RH, Yang SC, Chen YY, Chen PS, et al. The therapeutic effect of switching from tacrolimus to low-dose cyclosporine A in renal transplant recipients with BK virus nephropathy. Biosci Rep. 2019; 39: BSR20182058.
14. Nankivell BJ, Renthawa J, Sharma RN, Kable K, O'Connell PJ, Chapman JR. BK virus nephropathy: Histological evolution by sequential pathology. Am J Transplant. 2017; 17: 2065-2077.
15. Theodoropoulos N, Wang E, Penugonda S, Ladner DP, Stosor V, Leventhal J, et al. BK virus replication and nephropathy after alemtuzumab-induced kidney transplantation. Am J Transplant. 2013; 13: 197-206.
16. Huang G, Wu LW, Yang SC, Fei JG, Deng SX, Li J, et al. Factors influencing graft outcomes following diagnosis of polyomavirus-associated nephropathy after renal transplantation. PLoS One. 2015; 10: e0142460.
17. Yooprasert P, Rotjanapan P. BK virus-associated nephropathy: Current situation in a resource-limited country. Transplant Proc. 2018; 50: 130-136.
18. Imlay H, Whitaker K, Fisher CE, Limaye AP. Clinical characteristics and outcomes of late-onset BK virus nephropathy in kidney and kidney-pancreas transplant recipients. Transpl Infect Dis. 2018; 20: e12928.
19. Gardner SD. Prevalence in England of antibody to human polyomavirus (BK). Br Med J. 1973; 1: 77-78.
20. 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: 1019-1026.
21. Rinaldo CH, Tylden GD, Sharma BN. The human polyomavirus BK (BKP yV): Virological background and clinical implications. Apmis. 2013; 121: 728-745.
22. Abend JR, Jiang M, Imperiale MJ. BK virus and human cancer: Innocent until proven guilty. Semin Cancer Biol. 2009; 19: 252-260.

23. Sharma SG, Nickeleit V, Herlitz LC, de Gonzalez AK, Stokes MB, Singh HK, et al. BK polyoma virus nephropathy in the native kidney. Nephrol Dial Transplant. 2013; 28: 620-631.
24. Meylan E, Tschopp J. Toll-like receptors and RNA helicases: Two parallel ways to trigger antiviral responses. Mol Cell. 2006; 22: 561-569.
25. Al-Lamki RS, Wang J, Vandenabeele P, Bradley JA, Thiru S, Luo D, et al. TNFR1- and TNFR2-mediated signaling pathways in human kidney are cell type-specific and differentially contribute to renal injury. FASEB J. 2005; 19: 1637-1645.
26. Furmaga J, Kowalczyk M, Furmaga-Rokou O, Rokos CA, Zapolski T, Krakowski L, et al. Genotypes and variants of BKPyV in organ donors after brain death. Int J Mol Sci. 2022; 23: 9173.
27. Hirsch HH, Brennan DC, Drachenberg CB, Ginevri F, Gordon J, Limaye AP, et al. Polyomavirus-associated nephropathy in renal transplantation: Interdisciplinary analyses and recommendations. Transplantation. 2005; 79: 1277-1286.
28. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant. 2009; 9: S1-S155.
29. Hirsch HH, Randhawa P, AST Infectious Diseases Community of Practice. BK polyomavirus in solid organ transplantation. Am J Transplant. 2013; 13: 179-188.
30. Imlay H, Baum P, Brennan DC, Hanson KE, Hodges MR, Hodowanec AC, et al. Consensus definitions of BK polyomavirus nephropathy in renal transplant recipients for clinical trials. Clin Infect Dis. 2022; 75: 1210-1216.
31. Zakaria ZE, Elokely AM, Ghorab AA, Bakr AI, Halim MA, Gheith OA, et al. Screening for BK viremia/viruria and the impact of management of BK virus nephropathy in renal transplant recipients. Exp Clin Transplant. 2019; 17: 83-91.
32. Menter T, Mayr M, Schaub S, Mihatsch MJ, Hirsch HH, Hopfer H. Pathology of resolving polyomavirus-associated nephropathy. Am J Transplant. 2013; 13: 1474-1483.
33. Nickeleit V, Singh HK, Randhawa P, Drachenberg CB, Bhatnagar R, Bracamonte E, et al. The Banff working group classification of definitive polyomavirus nephropathy: Morphologic definitions and clinical correlations. J Am Soc Nephrol. 2018; 29: 680-693.
34. Yan L, Guo H, Han L, Huang H, Shen Y, He J, et al. Sternheimer-malbin staining to detect decoy cells in urine of 213 kidney transplant patients. Transplant Proc. 2020; 52: 823-828.
35. Hirt-Minkowski P, Handschin J, Stampf S, Hopfer H, Menter T, Senn L, et al. Randomized trial to assess the clinical utility of renal allograft monitoring by urine CXCL10 chemokine. J Am Soc Nephrol. 2023; 34: 1456-1469.
36. Weseslindtner L, Hedman L, Wang Y, Strassl R, Helanterä I, Aberle SW, et al. Longitudinal assessment of the CXCL10 blood and urine concentration in kidney transplant recipients with BK polyomavirus replication-a retrospective study. Transpl Int. 2020; 33: 555-566.
37. Haller J, Diebold M, Leuzinger K, Wehmeier C, Handschin J, Amico P, et al. Urine CXCL10 to assess BK polyomavirus replication after kidney transplantation. Transplantation. 2023; 107: 2568-2574.
38. Wen J, Sun R, Yang H, Ran Q, Hou Y. Detection of BK polyomavirus-associated nephropathy using plasma graft-derived cell-free DNA: Development of a novel algorithm from programmed monitoring. Front Immunol. 2022; 13: 1006970.

39. Drachenberg CB, Hirsch HH, Papadimitriou JC, Gosert R, Wali RK, Munivenkatappa R, et al. Polyomavirus BK versus JC replication and nephropathy in renal transplant recipients: A prospective evaluation. Transplantation. 2007; 84: 323-330.
40. Gras J, Nere ML, Peraldi MN, Bonnet-Madin L, Salmona M, Taupin JL, et al. BK virus genotypes and humoral response in kidney transplant recipients with BKV associated nephropathy. Transpl Infect Dis. 2023; 25: e14012.
41. Siripoon T, Apiwattanakul N, Mongkolrattanakul P, Tongsook C, Unwanatham N, Hongeng S, et al. Clinical and immunological characteristics for BK polyomavirus-associated nephropathy after kidney transplantation. Immun Inflamm Dis. 2023; 11: e956.
42. Sawinski D, Trofe-Clark J. BK virus nephropathy. Clin J Am Soc Nephrol. 2018; 13: 1893-1896.
43. Halim MA, Al-Otaibi T, Gheith O, Mosaad A, Zakaria Z, Said T, et al. Long-term follow-up of active treatment versus minimization of immunosuppressive agents in patients with BK virus-associated nephropathy after kidney transplant. Exp Clin Transplant. 2016; 14: 58-65.
44. Jahdali S, Al Oudah N, Alsaad KO, Kfoury H, Qurashi S, Al Sayyari A. Biopsy-proven BK virus-associated nephropathy: Clinico-pathologic correlations. Exp Clin Transplant. 2017; 15: 289-294.
45. Sommerer C, Suwelack B, Dragun D, Schenker P, Hauser IA, Witzke O, et al. An open-label, randomized trial indicates that everolimus with tacrolimus or cyclosporine is comparable to standard immunosuppression in de novo kidney transplant patients. Kidney Int. 2019; 96: 231-244.
46. Solis M, Velay A, Porcher R, Domingo-Calap P, Soulier E, Joly M, et al. Neutralizing antibody-mediated response and risk of BK virus-associated nephropathy. J Am Soc Nephrol. 2018; 29: 326-334.
47. Simard-Meilleur MC, Bodson-Clermont P, St-Louis G, Pâquet MR, Girardin C, Fortin MC, et al. Stabilization of renal function after the first year of follow-up in kidney transplant recipients treated for significant BK polyomavirus infection or BK polyomavirus-associated nephropathy. Transpl Infect Dis. 2017; 19: e12681.
48. Kawanishi K, Honda K, Koike J, Hattori M, Fuchinoue S, Tanabe K, et al. A preliminary study into the significance of intrarenal reflux in BK virus nephropathy after kidney transplantation. Transplant Direct. 2016; 2: e64.
49. Masutani K, Tsuchimoto A, Matsukuma Y, Kurihara K, Nishiki T, Kitada H, et al. Temporal serum creatinine increase and exacerbation of tubulointerstitial inflammation during the first two months in resolving polyomavirus BK nephropathy. Nephrology. 2015; 20: 45-50.
50. Shen CL, Yang AH, Lien TJ, Tarng DC, Yang CY. Tacrolimus blood level fluctuation predisposes to coexisting BK virus nephropathy and acute allograft rejection. Sci Rep. 2017; 7: 1986.
51. Saláková M, Ludvíková V, Hamšíková E, Kolářová M, Šroller V, Viklický O, et al. Pretransplantation seroreactivity in kidney donors and recipients as a predictive factor for posttransplant BKPyV-DNAemia. Front Immunol. 2022; 13: 929946.
52. Bae H, Jung S, Chung BH, Yang CW, Oh EJ. Pretransplant BKV-IgG serostatus and BKV-specific ELISPOT assays to predict BKV infection after kidney transplantation. Front Immunol. 2023; 14: 1243912.
53. Schaub S, Hirsch HH, Dickenmann M, Steiger J, Mihatsch MJ, Hopfer H, et al. Reducing immunosuppression preserves allograft function in presumptive and definitive polyomavirus-associated nephropathy. Am J Transplant. 2010; 10: 2615-2623.

54. Mindlova M, Boucek P, Saudek F, Jedinakova T, Voska L, Honsova E, et al. Kidney retransplantation following graft loss to polyoma virus-associated nephropathy: An effective treatment option in simultaneous pancreas and kidney transplant recipients. Transpl Int. 2008; 21: 353-356.
55. 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. 2010; 10: 1312-1315.
56. Leeaphorn N, Thongprayoon C, Chon WJ, Cummings LS, Mao MA, Cheungpasitporn W. Outcomes of kidney retransplantation after graft loss as a result of BK virus nephropathy in the era of newer immunosuppressant agents. Am J Transplant. 2020; 20: 1334-1340.
57. Johnston O, Jaswal D, Gill JS, Doucette S, Fergusson DA, Knoll GA. Treatment of polyomavirus infection in kidney transplant recipients: A systematic review. Transplantation. 2010; 89: 1057-1070.
58. Sener A, House AA, Jevnikar AM, Boudville N, McAlister VC, Muirhead N, et al. Intravenous immunoglobulin as a treatment for BK virus associated nephropathy: One-year follow-up of renal allograft recipients. Transplantation. 2006; 81: 117-120.
59. Lebreton M, Esposito L, Mengelle C, Del Bello A, Delarche A, Dörr G, et al. A 3-month course of ciprofloxacin does not prevent BK virus replication in heavily immunosuppressed kidney-transplant patients. J Clin Virol. 2016; 79: 61-67.
60. Baek CH, Kim H, Yu H, Yang WS, Han DJ, Park SK. Risk factors of acute rejection in patients with BK nephropathy after reduction of immunosuppression. Ann Transplant. 2018; 23: 704-712.
61. Rasaei N, Malekmakan L, Gholamabbas G, Abdizadeh P. Comparative study of intravenous immunoglobulin and leflunomide combination therapy with intravenous immunoglobulin single therapy in kidney transplant patients with BK virus infection: Single-center clinical trial. Exp Clin Transplant. 2023; 21: 814-819.
62. Benotmane I, Solis M, Velay A, Cognard N, Olagne J, Gautier Vargas G, et al. Intravenous immunoglobulin as a preventive strategy against BK virus viremia and BKV-associated nephropathy in kidney transplant recipients-results from a proof-of-concept study. Am J Transplant. 2021; 21: 329-337.
63. Sato N, Shiraki A, Mori KP, Sakai K, Takemura Y, Yanagita M, et al. Preemptive intravenous human immunoglobulin G suppresses BK polyomavirus replication and spread of infection in vitro. Am J Transplant. 2024; 24: 765-773.