AMERICAN SOCIETY FOR MICROBIOLOGY | Clinical Microbiology Reviews®

REVIEW

BK Polyomavirus: Clinical Aspects, Immune Regulation, and Emerging Therapies

George R. Ambalathingal,[a,d] Ross S. Francis,[b,d] Mark J. Smyth,[a,c,d] Corey Smith,[a] Rajiv Khanna[a]

QIMR Berghofer Centre for Immunotherapy and Vaccine Development, Tumour Immunology Laboratory, QIMR Berghofer Medical Research Institute, Herston, QLD, Australia[a]; Department of Nephrology, Princess Alexandra Hospital, Woolloongabba, QLD, Australia[b]; Immunology in Cancer and Infection Laboratory, QIMR Berghofer Medical Research Institute, Herston, QLD, Australia[c]; Faculty of Medicine, University of Queensland, Brisbane, QLD, Australia[d]

Published 22 February 2017

Citation Ambalathingal GR, Francis RS, Smyth MJ, Smith C, Khanna R. 2017. BK polyomavirus: clinical aspects, immune regulation, and emerging therapies. Clin Microbiol Rev 30:503–528. https://doi.org/10.1128/CMR.00074-16.

Address correspondence to Rajiv Khanna, rajiv.khanna@qimrberghofer.edu.au.

G.R.A. and R.S.F. contributed equally to this article.

SUMMARY BK polyomavirus (BKV) causes frequent infections during childhood and establishes persistent infections within renal tubular cells and the uroepithelium, with minimal clinical implications. However, reactivation of BKV in immunocompromised individuals following renal or hematopoietic stem cell transplantation may cause serious complications, including BKV-associated nephropathy (BKVAN), ureteric stenosis, or hemorrhagic cystitis. Implementation of more potent immunosuppression and increased posttransplant surveillance has resulted in a higher incidence of BKVAN. Antiviral immunity plays a crucial role in controlling BKV replication, and our increasing knowledge about host-virus interactions has led to the development of improved diagnostic tools and clinical management strategies. Currently, there are no effective antiviral agents for BKV infection, and the mainstay of managing reactivation is reduction of immunosuppression. Development of immune-based therapies to combat BKV may provide new and exciting opportunities for the successful treatment of BKV-associated complications.

KEYWORDS B cell responses, T cells, T cell immunity, immunotherapy, natural killer cells, pathogenesis, transplant, virus

INTRODUCTION

BK polyomavirus (BKV) is a member of the *Polyomaviridae* family of double-stranded DNA (dsDNA) viruses. Different members of the family infect different species of mammals, primates, rodents, and birds. The list of human polyomaviruses has evolved over the past 2 decades (Fig. 1). BKV was first isolated from an immunosuppressed renal transplant recipient with ureteric stenosis in 1971 (1) and is named after the initials of this individual (1, 2). BKV causes a common childhood infection without major clinical sequelae, and >80% of adults are seropositive for BKV (3, 4). After primary infection, BKV remains dormant and does not cause significant morbidity in healthy individuals (5). Clinically significant reactivation of latent BKV occurs in some immunosuppressed individuals, such as following HIV infection or transplantation (6). Kidney transplant recipients (KTRs) comprise the patient population that most frequently experiences complications of BKV reactivation, and a median of 19.5% of KTRs experience BK viremia posttransplantation. A proportion of these recipients will go on to develop BKV-associated nephropathy (BKVAN), which is associated with a significant risk of allograft loss (6–8). In addition, hemorrhagic cystitis (HC) is a well-recognized BKV-associated complication in hematopoietic stem cell transplant (HSCT) recipients (9).

EPIDEMIOLOGY AND TISSUE TROPISM

Primary infection with BKV occurs during early childhood, and studies have shown that 70% of children are infected with BKV by the age of 10 years; however, the route of transmission remains unclear (4). The primary mode of transmission is speculated to be via a respiratory route, as supported by evidence of BKV infection in the respiratory tract and tonsils of children; however, other routes of transmission are also proposed (Table 1). Primary infection is usually asymptomatic or, rarely, causes a mild respiratory illness (10). It has been suggested that BKV enters the bloodstream via infected tonsillar tissue, thereby infecting peripheral blood mononuclear cells and disseminating virus to secondary sites of infection, including the kidney (3). Following resolution of primary infection, BKV persists primarily in kidney epithelial cells for life, with occasional reactivation manifesting as asymptomatic viruria (11). BKV has also been found in leukocytes, the brain, and lymph nodes, as evidenced by the presence of BKV DNA (3, 12). Viral shedding in urine is more common for immunocompromised patients than for healthy individuals (13). The mechanism of viral persistence and the conditions that lead to viral reactivation upon immunosuppression are still unclear.

VIRION STRUCTURE

Members of the *Polyomaviridae* family demonstrate structural similarity, with similar capsid sizes, high levels of genetic homology, and comparable genome sizes. BKV has a small, nonenveloped, icosahedral capsid with a diameter of 40 to 44 nm comprised of the virus-encoded capsid proteins VP1, VP2, and VP3 (14) (Fig. 2). The capsid proteins surround a single molecule of DNA complexed with histone proteins in the form of chromatin chains. The capsid proteins are arranged in a T=7 icosahedral structure containing 360 molecules of VP1 organized into 72 pentamers. Each pentamer is linked to a single moiety of the minor capsid proteins, VP2 and VP3, internally (Fig. 2). Therefore, VP1 is the only viral protein exposed on the outside of the virion and is responsible for attachment of the virus to host cell receptors that aid in entry of virus into the cell. In a recent study of BKV structure by use of cryo-electron microscopy, Hurdiss et al. showed that the minor capsid proteins (VP2 and VP3) have discrete points of contact with the histones and genomic DNA (Fig. 2) (15). They also proposed a model in which the minor capsid proteins could act as a bridge between VP1 and the chromatinized viral DNA; however, the significance of such contact with the genomic DNA has yet to be studied.

MECHANISM OF CELL ENTRY

BKV entry into host cells is mediated via caveolae, unlike that of other polyomaviruses, which typically use clathrin-mediated entry (Fig. 3). VP1 has a cleft between the

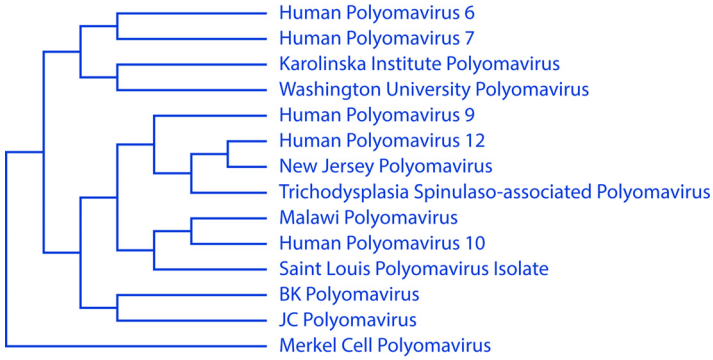

FIG 1 Phylogenetic tree showing the distances of relationships between the human polyomaviruses discovered to date.

β-strand C1 (BC1) and BC2 loops that can bind to α2-8-linked disialic acid motifs on gangliosides GD1b and GT1b expressed on host cell membranes (16–19). Entry into the cell is then driven by a caveola-mediated endocytic pathway (16, 20). Following internalization, BKV is carried toward the endoplasmic reticulum by use of microtubules, from which it follows the classical endocytic pathway for capsid uncoating (21, 22). VP2 and VP3 mediate the entry of BKV into the nucleus via importin after the uncoating of VP1 (23–25). After entering the nucleus, the BKV genome remains episomal in human cells, in contrast to the integration of the BKV genome into host DNA of rodent cells, which leads to the development of tumors in rodents (26–28). While little is known about the mechanism of integration of BKV DNA into rodent genomic DNA leading to malignancy, it would be interesting to study the factors involved in such transformation. These may provide insights into the involvement of BKV in oncogenesis in humans, which is higly debated.

GENOMIC STRUCTURE AND REPLICATION

The BKV genome is approximately 5,300 bp long and contains genes coding for the structural proteins (VP1, VP2, and VP3) and the viral replication proteins (large T antigen [LTA], small T antigen [STA], and agnoprotein) and a noncoding control region (NCCR) (Fig. 4). The length of the genome varies in individual variants due to the alterations in the NCCR. The NCCR is a hypervariable region containing various binding sites for host cellular regulatory factors, and hence it is also referred to as the hypervariable regulatory region (HVRR) (26, 29, 30). The open reading frame is situated in the center of the genome such that replication can proceed in a bidirectional way (31) (Fig. 4). The early coding regions are transcribed before the start of replication, promoting the expression of LTA and STA. These antigens accumulate in the nucleus and help in the replication of viral DNA (32, 33). During the viral DNA replication process, LTA forms a multimeric complex which binds to the origin of replication and acts like a helicase to facilitate the transcription of late coding regions (34, 35). LTA is also a key regulatory molecule driving the host cell to S phase of the cell cycle by binding to the tumor suppressor proteins Rb, p107, p130, and p53 (30, 36–38). Based on studies with simian virus 40 (SV40), STA is involved in viral replication, cell cycle progression, and transformation

TABLE 1 Route of transmission of BKV

Route of transmission	Source of BKV identification	Reference(s)
Respiratory	Upper respiratory tract	10
	Tonsils	10
	Waldeyer's ring	232
Fecal-oral	BKV DNA in sewage	233
Blood transfusion	Leukocytes	3
Transplacental	Fetus	234–236

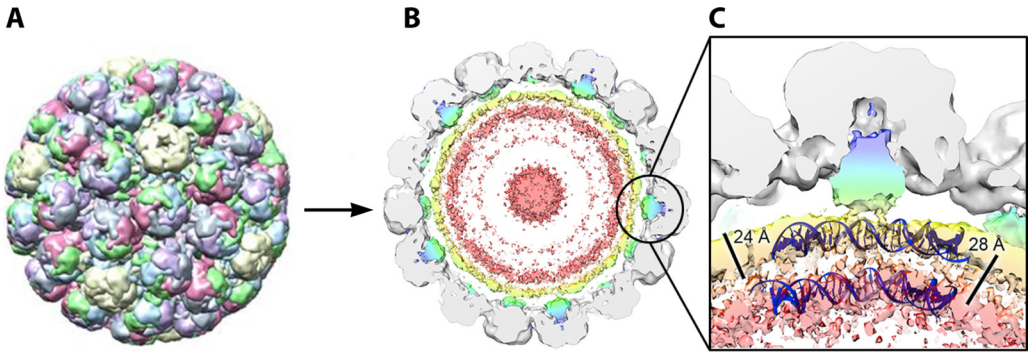

FIG 2 Cryo-electron microscopy structure of BKV, showing an external view, minor capsid proteins, and genome organization. (A) External view of the virion at a contour level of 0.022. The electron density maps were sharpened using a negative B factor correction (B = −456 and −804 Å^2). (B) View of a 40-Å-thick slab through the unsharpened/unmasked virion map, shown at a contour level of 0.0034. Pyramidal density below each VP1 penton and two shells of electron density adjacent to the inner capsid layer can be seen. The density within 6 Å of the fitted coordinates for SV40 VP1 is colored gray. The remaining density is colored in a radial color scheme. Densities for VP2 and VP3 are colored blue and green, and those for packaged dsDNA are yellow and pink. (C) Enlarged view of the pyramidal density beneath a single VP1 penton of the virion, shown at a contour level of 0.0032. Strands of dsDNA wrapped around a human histone octamer (PDB entry 1AOI) are shown, indicating that the two shells of density have comparable spacings. A discrete connective density between the pyramidal density and internal shells is also apparent. (Adapted from reference 15 [published under a Creative Commons {CC BY} license].)

(39–41). The late coding regions are expressed only after the onset of viral DNA replication, as they code for structural proteins involved in viral packaging as well as the agnoprotein (26). The viral capsid proteins, VP1, VP2, and VP3, are produced in the cytoplasm and recruited into the nucleus by use of the nuclear localization signals attached to the proteins. Once the capsid proteins enter the nucleus, viral assembly occurs and the viral progenies accumulate in the nucleus (42, 43).

BKV GENOTYPES AND VARIANTS

BKV can be categorized into four genotypes based on sequence variation in the genomic region of VP1 (44, 45). Serological studies indicate that BKV genotype I has the highest prevalence in the human population, followed by genotype IV. Genotypes II and III are found to infect only a minority of adults. BKV genotype I is further classified into four subgroups: subgroups Ia, Ib1, Ib2, and Ic (46, 47). BKV genotype IV can be further subgrouped into subgroups IVa1, IVa2, IVb1, IVb2, IVc1, and IVc2 (48). The distribution pattern of each of the genotypes has been studied extensively. Genotype I viruses are present worldwide, while genotype IV is found in northeastern Asia and Europe (46–51). The clinical and immunological implications of infection with the different genotypes of BKV are still unknown. Apart from the genotypes based on the variation in the VP1 region, there are also two other forms of BKV due to the variation in the NCCR, namely, archetype (ww) and rearranged (rr) variants. Archetypal BKV contains a linear block of O-P-Q-R-S, where O represents the origin of replication and P-Q-R-S represents promoters and regulatory regions of early and late coding regions (52). Deletion and duplications in the NCCR pattern sequences occur due to the continuous replication of the viral DNA during reactivation, leading to the generation of the rearranged variant viruses (53). These genetic variants of BKV are commonly found in individuals with BKV-associated diseases along with the archetypal BKV. While preliminary studies have suggested that these variations and rearrangements are not involved in the development of BKV-associated diseases (52, 54), more detailed studies on the genetic variants of the NCCR in disease development are required. Furthermore, it is also important to appreciate that BKV can persist in many tissues throughout the body, and analysis of viral sequences from renal tissue and serum alone may miss potential sources of pathogenic virus within other tissue reservoirs (e.g., the central nervous system [CNS] and lymph nodes). Analysis of viral sequences from these tissues may reveal novel BKV genotypes and variants which correlate wth disease development.

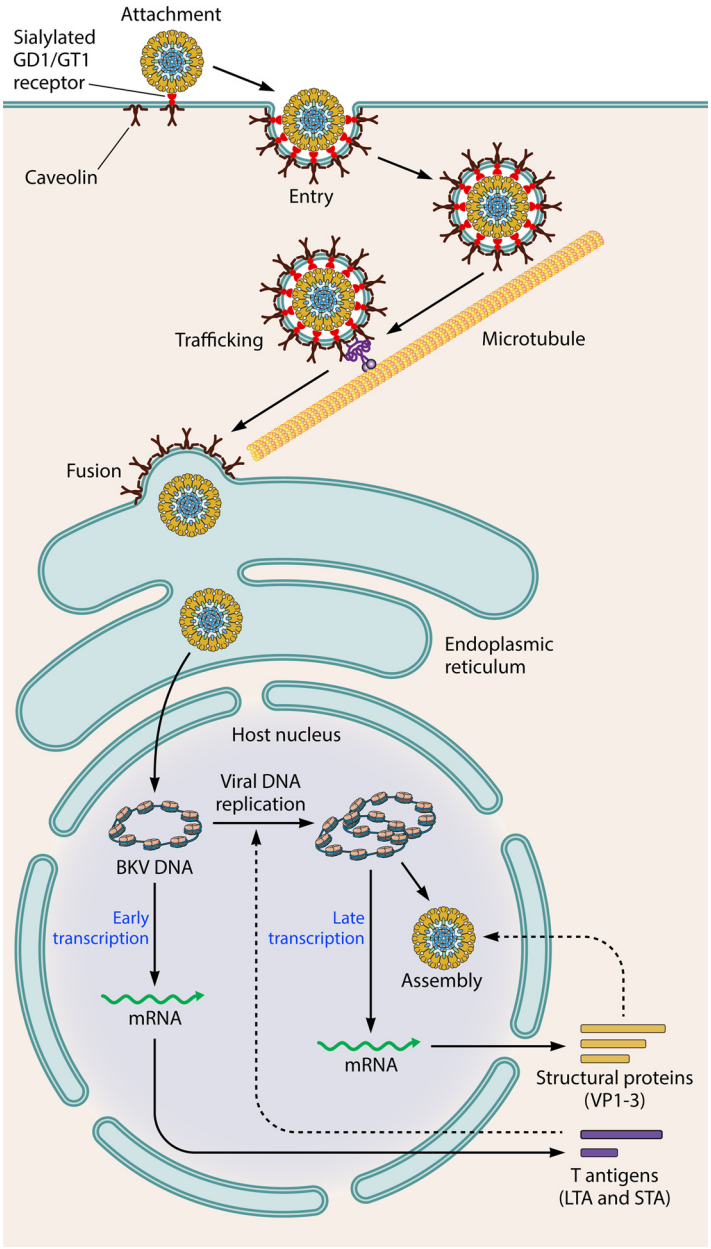

FIG 3 Schematic outline of BKV entry into host cells. For caveola-mediated entry of BKV into host cells, attachment of VP1 to the ganglioside receptors GD1 and GT1 initializes the internalization of BKV through caveola formation. The caveola encapsulating the virus then translocates in the cytoplasm with the help of microtubules. The virus then fuses with the endoplasmic reticulum (ER), where the VP1 layer disassembles. The virus then enters the host nucleus and lies episomally. In the nucleus, the early coding regions are transcribed first, which regulates the transcription of late coding regions.

VIRAL PERSISTENCE

BKV establishes lifelong persistent infection in the host. It is still unclear whether BKV stays latent in the host cell or maintains a low level of gene expression with persistent infection. The mechanism of latency is well studied for herpesviruses, which has highlighted the regulation of various genes controlling viral lytic replication (55). BKV encodes microRNAs (miRNAs) similar to those of herpesviruses, which act as regulators of viral replication. Recently, Broekema and Imperiale showed that a high level of expression of miRNA complementary to the 3′ end of the *LTA* mRNA is responsible for control of BKV replication (Fig. 4) (56). Further studies have shown that miRNA expression suppresses the autoregulation of viral replication (57). While no other mechanism

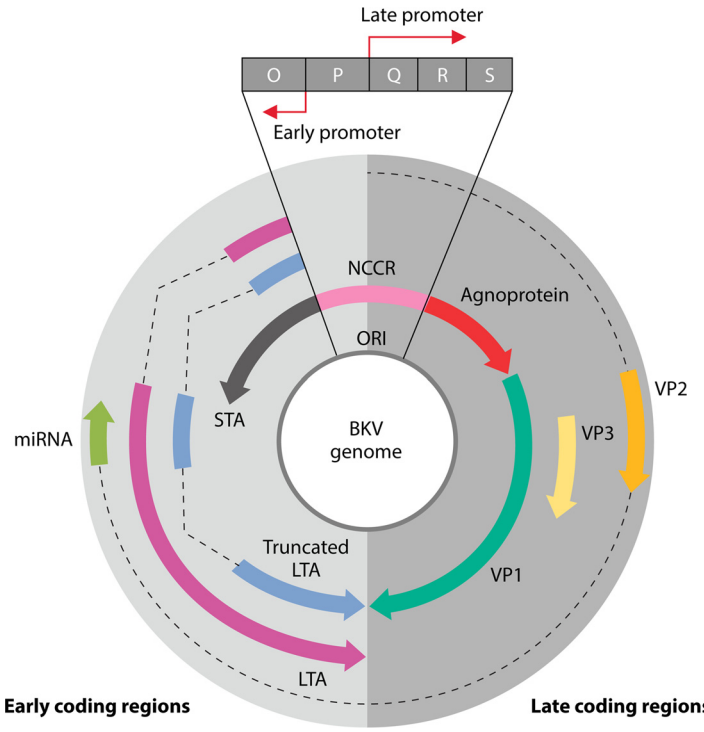

FIG 4 Genome stucture of BKV. The transcription of both early and late coding regions proceeds in a bidirectional way from the origin of replication (ORI) within the noncoding control region (NCCR). The transcriptional splicing regions are represented by dashed lines. The late coding regions encode structural proteins (VP1, VP2, and VP3), while the early coding regions transcribe the tumorigenic proteins (LTA and STA). The late coding regions also encode the nonimmunogenic agnoprotein. The expression of miRNA complementary to the 3′ end of LTA has been shown to be involved in replication control of BKV.

of latency has yet been reported, the evidence regarding the association of miRNA with latency is promising and requires more detailed research.

IMMUNE RESPONSES TO BKV

Innate Immune Response

While a few studies have investigated the interaction of BKV and the innate immune system, there are few data regarding the role that innate immune mediators play in controlling BKV infection. Most studies have focused upon settings of viral reactivation and disease (BKVAN) in KTRs. Womer and colleagues showed a role for dendritic cells (DCs) in BKVAN, demonstrating a reduced number of DCs in the peripheral blood of renal transplant recipients with BKVAN. Further studies demonstrated that patients with fewer DCs before transplantation are at a higher risk of BKVAN (58). DCs also likely play a critical role in promoting the induction of the adaptive immune response, particularly the generation of BKV-specific T cells. Using a mouse model of BKVAN, Drake and colleagues showed that an increased number of DCs *in vivo* correlated with an enhanced magnitude of virus-specific $CD8^+$ T cells (59, 60). These studies strongly suggest that DC activation likely plays an important role in priming protective immune responses against BKV; however, the mechanisms of DC activation following BKV encounter remain unclear. Unlike those of other polyomaviruses, the VP1 protein of BKV does not induce strong maturation of DCs (61).

Natural killer (NK) cells are also likely to play a role in controlling BKV infection in KTRs. Bohl and colleagues showed that the absence of HLA C7 from the donor or recipient was associated with an increased risk of viremia (62). While the precise mechanism for this association still remains unclear, more recent observations by Trydzenskaya et al. proposed a role for killer cell immunoglobulin-like receptors (KIR) in

the immune defense against BKV. They found that patients with BKVAN had a small number of activating KIR, in particular those of the KIR3DS1 genotype, in NK cells compared to the control group (63). Recent studies showed that BKV immune evasion strategies may be mediated via the inhibition of NK cell recognition. Bauman demonstrated that BKV produces miRNAs which can suppress the expression of the stress-induced ligand ULBP3, which is recognized by the NKG2D receptor on NK cells, thereby avoiding NK cell-mediated cytotoxicity (64).

Other innate mediators have been shown to contribute to BKV control. Defensins are key mediators of innate immunity, exhibiting antimicrobial activity against a wide range of viruses, fungi, and bacteria. Dugan et al. showed that human α defensin 5 (HD5) inhibits binding of BKV to host cells by aggregating viruses, thereby blocking binding of viruses to the cells (65). HD5 is commonly found in the urogenital tract, which is also the resident site of BKV, and it was demonstrated that HD5 could neutralize BKV in a serum-independent manner, suggesting that it may play an important role in mediating asymptomatic reactivation of BKV in the urogenital tract.

Innate immune mediators also likely play a role in graft loss in KTRs with BKVAN. BKVAN is associated with renal inflammation, the increased expression of interleukin-6 (IL-6), IL-8/CXCL8, RANTES/CCL5, MCP-1/CCL2, and IP-10/CXCL10 in kidney biopsy specimens (66), and an upregulation of two proinflammatory genes, encoding pentraxin 3 (PTX3), a cytokine-inducible protein, and MICB, which interacts with NKG2D receptors on NK cells during BKV infection in kidney proximal tubular cells (67). Furthermore, it has been shown that the microenvironment due to BKV infection promotes graft fibrosis in BKVAN patients, which is evidenced by the increased expression of matrix collagens, transforming growth factor beta (TGF-β), and MMP2 and -9, as well as markers of epithelial-mesenchymal transformation (EMT), in BKVAN biopsy specimens (68).

Adaptive Immune Response

Humoral response. Adaptive immune responses against viruses typically develop soon after initial exposure to viral antigens. BKV is usually encountered early in childhood, which induces BKV-specific neutralizing antibody responses. In a study of healthy individuals, Egli and coworkers found BKV-specific IgG antibodies in 87% (87 of 100 individuals) of younger individuals (aged 20 to 29 years) and 71% (71 of 100 individuals) of older individuals (aged 50 to 59 years) (69). Similarly, Randhawa and colleagues found that 80% (57 of 71 individuals) of kidney donors had IgG antibodies and 22% (16 of 71 individuals) had IgA antibodies specific to BKV (70). Reports suggest that the presence of BKV-specific antibodies alone does not provide protection against BKV reactivation and associated diseases (71).

In most viral infections, antibodies serve as neutralizing agents by various mechanisms, one of which is attachment of antibodies to viral receptors, thereby restricting further infection by the virus. Mutations in viral receptors can cause escape from antibody-mediated neutralization (72–74). Pastrana and colleagues recently showed that certain BKV genotypes can escape neutralization from antibody raised against another genotype due to variation in antibody receptor binding (75). The same group had earlier postulated that KTRs who lack antibodies capable of neutralizing a wider range of BKV serotypes are at greater risk of graft rejection (76). These results suggest that developing cross-neutralizing antibodies that can act on different BKV genotypes may be a potential strategy to restrict BKV infection before immunosuppression therapy in KTRs. Uncontrolled replication of BKV in the kidney during BKVAN results in an increase in the viral load in blood, which in turn can induce a higher humoral response. Although BKV-specific antibody responses likely play an important role in neutralizing circulating virus, antibody alone is unable to control persistent latent infection (71). Similar to all persistent viral infections, the efficient control of latent viral reactivation is most likely dependent upon the induction of stable antiviral memory T cell responses.

T cell responses. Recent studies have begun to elucidate the important role of T cells in controlling BKV infection. It has been demonstrated that in KTRs, reconstitution of BKV-specific T cells is associated with better control of viruria and viremia (8, 71, 77–81). These studies indicate that immune control is dependent on both $CD4^+$ and $CD8^+$ T cells (82) and correlates with the frequency of polyfunctional BKV-specific T cells (83). This suggests that monitoring the frequency of BKV-specific T cells following transplantation may provide a strategy to predict the risk of viral reactivation and BKVAN, as shown previously for T cell responses to human cytomegalovirus (CMV) in transplant recipients (84). Analysis of the T cell responses from BKV-seropositive individuals has shown that BKV-specific T cell responses can be detected against all five BKV proteins in both seropositive healthy individuals and transplant patients (77, 79–81, 85–88). T cells specific for VP1 and LTA are most frequently detected in BKV-infected individuals (89, 90). While BKV-specific $CD4^+$ and $CD8^+$ T cells can be detected in healthy individuals and in KTRs, it has been suggested that the T cell response to BKV is mediated predominantly by $CD4^+$ T cells (87, 88, 91). Recent reports have shown that $CD4^+$ T cells likely have a direct role in controlling BKV infection, mediated through the expression of proinflammatory cytokines, including gamma interferon (IFN-γ) and tumor necrosis factor (TNF), and via the expression of the cytolytic molecule granzyme B (92). These studies also suggest that $CD4^+$ T cells can control BKV reactivation even in the absence of $CD8^+$ T cell immunity (92). More recently, the same group reported that the frequency of $CD4^+$ T helper cells significantly increased before and after the clearance phase, while cytolytic $CD4^+$ cells increased during the clearance phase (93). They also reported that immunosuppressant (IS) drugs used to prevent graft rejection in KT patients can cause a reduction in the expression of cytokines, such as IFN-γ and TNF, by BKV-specific T cells. Other studies of KTRs with active BKV replication showed that $CD8^+$ T cells were predominantly LTA specific, while VP1 elicited a mainly $CD4^+$ T cell response (81). Mueller and colleagues recently showed VP3 to be an antigenic target eliciting both $CD4^+$ and $CD8^+$ T cell responses in BKVAN patients (87).

Recent studies have also begun to investigate the presence of BKV-specific T cells in renal tissue and their association with BKVAN (94, 95). Zeng and colleagues tracked and quantitated BKV-specific T cells expanded from peripheral blood in renal allograft biopsy specimens with or without BKVAN (96). While T cell receptor analysis using next-generation sequencing revealed the presence of virus-specific T cells in biopsy specimens from patients with BK viremia or nephropathy, interestingly, these biopsy specimens contained 7 to 8 times more alloreactive T cell clones than virus-specific T cells. These observations suggest that the tissue injury during BKV-associated nephropathy is mediated primarily by the influx of bystander secondary T cells triggered by both alloreactive and virus-specific immunity.

One of the major roadblocks in studying BKV-specific T cells has been their low precursor frequency in the peripheral blood of both healthy volunteers and KTRs (79). Hence, most studies have used *in vitro*-expanded virus-specific T cells stimulated with antigenic peptide pools or BKV lysate. Typically, overlapping peptide pools (OPP) of BKV proteins have been used to stimulate T cells because BKV-specific T cell epitopes have not been characterized comprehensively (87, 91). Trydzenskaya et al. demonstrated that T cell stimulation using overlapping peptide pools of all five BKV antigens improved the sensitivity compared to that with single-antigen stimulation (91). This approach of using mixed peptide pools for BKV-specific T cell responses was also used by Mutlu et al. to attain maximum sensitivity for the quantitation of BKV-reactive $CD4^+$ T cells prior to or following transplantation (97).

A number of studies have identified potential $CD4^+$ and $CD8^+$ T cell determinants from BKV, although thorough investigations in a large cohort of healthy donors and kidney patients have not been undertaken (86, 88, 98–103). These early studies identified BKV-specific $CD8^+$ T cell epitopes restricted through HLA A1, A2, A3, A24, B7, and B8 (79, 86, 99, 101, 103, 104). A detailed list of $CD8^+$ T cell epitopes mapped from BKV is presented in Table 2. More recently, Cioni and colleagues employed a combination of bioinformatics and an *in vitro* expansion strategy to predict 9-mer epitopes

TABLE 2 List of HLA class I-restricted $CD8^+$ T cell epitopes mapped from BKV

Epitope sequence	Antigen	HLA restriction	Amino acid positions	Tested in healthy controls	Tested in transplant recipients	Reference(s)
MLTERFNHIL	LTA	HLA-A*02:01	362–370	Yes	Yes	85
VIFDFLHCI	LTA	HLA-A*02:01	406–414	Yes	Yes	85
FLHCIVFNV	LTA	HLA-A*02:01	410–418	Yes	Yes	85
LLMWEAVTV	VP1	HLA-A*02:01	108–116	Yes	Yes	79
AITEVECFL	VP1	HLA-A*02:01	44–52	Yes	Yes	79
LLLIWFRPV	LTA	HLA-A*02:01	579–587	Yes	yes	99, 103
LPLMRKAYL	LTA	HLA-B*07:02/B*08	27–35	Yes	Yes	99, 103
CLLPKMDSV	LTA	HLA-A*0201	398–406	Yes	No	99, 103
KLCTFSFLI	LTA	HLA-A*0201	216–224	Yes	No	99, 103
RLDSEISMY	LTA	HLA-A*0101	604–612	Yes	Yes	104
VSWKLITEY	LTA	HLA-A*0101	270–278	Yes	Yes	104
YSALTRDPY	LTA	HLA-A*0101	235–243	Yes	Yes	104
WSSSEVPTY	LTA	HLA-A*0101	77–85	Yes	Yes	104
FLICKGVNK	LTA	HLA-A*0301	222–230	No	Yes	104
ILYKKLMEK	LTA	HLA-A*0301	172–180	Yes	Yes	104
SVKVNLEKK	LTA	HLA-A*0301	506–514	Yes	Yes	104
RTLACFAVY	LTA	HLA-A*0301	156–164	Yes	Yes	104
ACFAVYTTK	LTA	HLA-A*0301	159–167	Yes	Yes	104
GVNKEYLLY	LTA	HLA-A*0301	227–235	No	Yes	104
IVFNVPKRR	LTA	HLA-A*0301	414–422	Yes	Yes	104
SAINNFCQK	LTA	HLA-A*0301	208–216	Yes	Yes	104
AWLHCLLPK	LTA	HLA-A*0301	394–402	No	Yes	104
AYLRKCKEF	LTA	HLA-A*2402	33–41	Yes	Yes	104
PYHTIEESI	LTA	HLA-A*2402	242–250	Yes	Yes	104
QYMAGVAWL	LTA	HLA-A*2402	388–396	Yes	Yes	104
VFLLLGMYL	LTA	HLA-A*2402	287–295	No	Yes	104
RYWLFKGPI	LTA	HLA-A*2402	422–430	No	Yes	104
RTLACFAVY	LTA	HLA-A*0101	156–164	No	Yes	105
GVNKEYLLY	LTA	HLA-A*01/A*11	227–235	No	Yes	105
DVFLLLGMY	LTA	HLA-A*0101	286–294	No	Yes	105
KLCTFSFLI	LTA	HLA-A*0201	216–224	No	Yes	105
MYLEFQYNV	LTA	HLA-A*0201	293–301	No	Yes	105
TLAAGLLDL	LTA	HLA-A*0201	436–444	No	Yes	105
ILYKKLMEK	LTA	HLA-A*0301	172–180	No	Yes	105
LLLGMYLEF	LTA	HLA-A*24/B*51	289–297	No	Yes	105
LERAAWGNL	LTA	HLA-B*0702	19–27	No	Yes	105
FPSDLHQFL	LTA	HLA-B*0702	140–148	No	Yes	105
MLTERFNHIL	LTA	HLA-B*0801	362–370	No	Yes	105
LLLIWFRPV	LTA	HLA-B*0801	579–587	No	Yes	105

from the BKV early viral gene region (105). These epitopes were specifically mapped for 14 major HLA class I alleles prevalent in Europe and North America. Using this highly innovative approach, Cioni et al. successfully expanded the list of BKV T cell epitopes to at least 39, among which 21 epitopes were further confirmed by HLA peptide streptamer staining (105). Sahoo et al. assessed genetic variability in sections of the BKV genome coding for T cell epitopes, demonstrating very limited variability (less than 5%) in a cohort of 65 samples (106). Cioni and colleagues demonstrated that some of the epitopes they identified shared strong homology with JC polyomavirus (JCV) (105). Similar observations have been seen in other studies investigating an overlap between BKV and JCV immunity (90, 98, 99). These studies also imply that prior JCV infection may induce T cell responses that cross-protect from BKV-associated diseases, and *vice versa*, due to the high level of homology between both viruses. These observations have defined the conserved nature of BKV immunity and its potential overlap with JCV, providing a platform for the development of a standardized immune monitoring protocol for BKV that may potentially be extended to include JCV. While this research has led to the determination of a significant number of BKV-specific T cell epitopes, it is imperative to expand these analyses to comprehensively map T cell epitopes within all five antigenic proteins of BKV and to expand the HLA restriction to alleles which are common in ethnic groups other than European and North American groups. This will

help in developing effective immune monitoring tools for BKV-associated diseases, particularly for regions with high rates of kidney transplantation outside Europe and North America.

CLINICAL AND LABORATORY DIAGNOSIS OF BKV INFECTION

BKV predominantly causes disease in immunocompromised patients. The major clinical manifestations are BKV-associated nephropathy (BKVAN) or ureteric stenosis in KTRs and HC, which is typically seen only in HSCT recipients. Other, less common clinical manifestations that have been linked to BKV infection include interstitial pneumonitis and meningoencephalitis (107–116). BKV-associated central nervous system infections are predominantly seen in patients who have an underlying immunodeficiency or comorbid illness, including HSCT or HIV infection. Clinical manifestations in these patients include headache, confusion, ataxia, dizziness, paraplegia, and seizures (114).

PCR-based viral load quantitation in the plasma, urine, or cerebrospinal fluid (for CNS infection) is the standard clinical tool for monitoring BKV reactivation (117). Several reports have shown that sustained viremia in the plasma of renal transplant patients is associated with a higher risk of BKVAN development (118–121). Although qualitative PCR is highly sensitive for detecting active viral replication, it has a relatively low positive predictive value (PPV) (30 to 50%) for BKVAN (120, 121). Studies reporting quantitative BKV PCR results demonstrate a positive correlation between higher viral loads and an increased probability of developing BKVAN. For example, in a prospective study of KTRs, Hirsch et al. found that all recipients with BKVAN had viral loads of $>$7,700 copies/ml (121). Based on this, a threshold of 1×10^4 copies/ml of BKV has been proposed as a threshold for improving the PPV, although the lack of a standardized protocol for BKV PCR assays has created difficulty in directly comparing viral loads between studies. However, the World Health Organization Expert Committee on Biological Standardization (ECBS) recently published an international standard for BKV PCR-based assays, which will hopefully lead to harmonization of BKV loads between laboratories (122).

More recently, measurement of BKV mRNA levels for the detection of active BKV replication was reported (123), and a noninvasive method to detect BKV mRNA levels in urine was shown to be highly specific and sensitive. The method showed 93.9% specificity using 6.5×10^5 BKV VP1 mRNAs/ng RNA in urinary cells as a cutoff limit (123, 124). Though this mRNA-based method for detecting BKV replication is promising, this method requires further validation as a tool for predicting patients who will develop more severe features of BKV infection, such as BKVAN. Singh and colleagues recently described a polyomavirus Haufen test as a noninvasive biomarker to predict BKVAN (125, 126). Haufen is the term used to describe BKV aggregates in the urine; cast-like three-dimensional BKV aggregates are detected using electron microscopy. This method is reported to have a high positive predictive value (more than 90%) for BKVAN (125). However, because the method has been published only as a single-center report, it requires further validation, and the assay is not feasible for routine clinical practice due to the cost and limited availability of electron microscopy.

BKV REACTIVATION IN KIDNEY TRANSPLANT RECIPIENTS

Evidence of BKV reactivation is frequently detected in kidney transplant recipients receiving contemporary immunosuppressive regimens, as summarized in Table 3. Although less common, there have also been reports of BKV reactivation and BKVAN occurring in recipients of nonrenal solid organ transplants (127, 128). Viruria or detection of urinary decoy cells is the most sensitive marker of BKV reactivation, occurring in 23 to 73% of KTRs (Table 3). BK viremia affects 8 to 62% of KTRs, with the peak incidence occurring at 3 to 6 months posttransplantation (95, 129), and the incidence of BKVAN in the first year posttransplantation is reported to be in the range of 1 to 7% (Table 3). The wide range of reported frequencies of BKV reactivation may be due to the extensive variation in immunosuppressive regimens utilized at different transplant

TABLE 3 Reported frequencies of BKV reactivation and BKVAN in kidney transplant recipients[a]

Study author(s), yr (reference)	Initial immunosuppression regimen	% of recipients with:				No. of recipients
		BK viruria/ decoy cells	BK viremia	Biopsy-confirmed BKVAN	Graft loss due to BKVAN	
Hirsch et al., 2002 (121)	T, A, P or C, M, P	23	10	5	Nil	78
Brennan et al., 2005 (129, 161)	ATG, T/C, M/A, P	35	12	Nil	Nil	200
Bessollette-Bodin et al., 2005 (13)	ATG/IL-2, T/C, P	57	29	Nil	Nil	104
Drachenberg et al., 2007 (153)	T, M, P	73	62	6	Nil	103
Dadhania et al., 2008 (237)	ATG/IL-2, T, M, ±P	NR	31	7	Nil	120
Almeras et al., 2011 (159)	ATG/IL-2, T/C/S, P	NR	11	<1	<1	119
Chakera et al., 2011 (134)	IL-2, T, A/M, P or AZM, T, M	18	8	1	Nil	313
Sood et al., 2012 (238)	ATG/IL-2, T, M, P	17	27	2	Nil	240
Barbosa et al., 2013 (239)	AZM/IL-2, R, IVIG, T, M, P	NR	20	2	<1	187
	ATG/IL-2, T/C, M, P	NR	10	1	<1	284
Borni-Duval et al., 2013 (147)	T/C, M, P	40	20	7	NR	240
Hirsch et al., 2013 (94)	IL-2, T/C, M, P	40	23	NR	NR	629
Schaub et al., 2010 (162)	IL-2/ATG, T/C, M, P/S	NR	19	6	Nil	203
Theodoropoulos et al., 2013 (152)	AZM/IL-2, T, M, ±P	38	12	5	1	666
Knoll et al., 2014 (194)	IL-2/ATG, T/C, M, P	NR	31	Nil	Nil	154
3C Study Collaborative Group et al., 2014 (151)	AZM, T, M	NR	7	1	Nil	426
	IL-2, T, M, P	NR	3	2	Nil	426
Schwarz et al., 2016 (240)		40	29	10	1	214
Sawinksi et al., 2015 (241)	ATG, T, M, P	NR	17	2	Nil	785
Wunderink et al., 2017 (142)	AZM/IL-2, T/C, M, P	NR	27	3	Nil	407

[a]T, tacrolimus; C, cyclosporine; A, azathioprine; M, mycophenolate; S, sirolimus; P, prednisolone; AZM, alemtuzumab; ATG, thymoglobulin; IL-2, basiliximab/daclizumab; R, rituximab; IVIG, intravenous immunoglobulin; NR, not reported.

centers, as well as to differences in frequency of monitoring and assay sensitivity (130). Clinically, BKV reactivation is asymptomatic, and if BKVAN occurs, this manifests as deterioration in allograft function (118, 121, 131, 132). As a consequence, most clinicians now screen KTRs prospectively for BKV reactivation, either by monitoring for decoy cells in urine or by quantitative PCR analysis of urine or peripheral blood for BKV detection (Table 4) (133–135). A definitive diagnosis of BKVAN requires a kidney biopsy, which is typically performed when BK viremia persistently exceeds 1×10^4 copies/ml

TABLE 4 Diagnostic testing and prognostic values for BKV infection and disease

Diagnostic method	Sensitivity for detection of BKV infection (%)	Specificity for detection of BKV infection (%)	Positive predictive value (PPV) for diagnosis of BKVAN (%)	Negative predictive value (NPV) for diagnosis of BKVAN (%)	Comment(s)	Reference(s)
Urine cytology for decoy cells	>80	70–84	20–35	>95	Useful for determining BKV reactivation but low PPV for BKVAN	120, 121, 242–244
Urine PCR	>98	78	30–40	>95	Effective at detecting possible BKVAN with BKV loads of $>1 \times 10^7$ copies/ml	118, 120, 245, 246
Serum PCR	90–100	83–96	50–80	>95	Highly specific and sensitive for detecting BKV reactivation; PPV for BKVAN increases with a higher BKV load; a cutoff of 1×10^4 copies/ml has been suggested as a threshold for biopsy specimens to exclude BKVAN	118, 120, 121, 243, 245, 246
Haufen detection (electron microscopy)	100	>95	>95	100	Higher reported PPV than that for any other method, but the method is expensive	125, 126
Histopathology			>98	100	Kidney biopsy is the gold standard for determining disease progression	140
					Stage/class A: infection/cytopathic changes, <25%; interstitial inflammation/tubular atrophy/fibrosis, <10%	94
					Stage/class B: infection/cytopathic changes, 11–50%; interstitial inflammation/tubular atrophy/fibrosis, <50%	
					Stage/class C: infection/cytopathic changes, >50%; interstitial inflammation/tubular atrophy/fibrosis, >50	

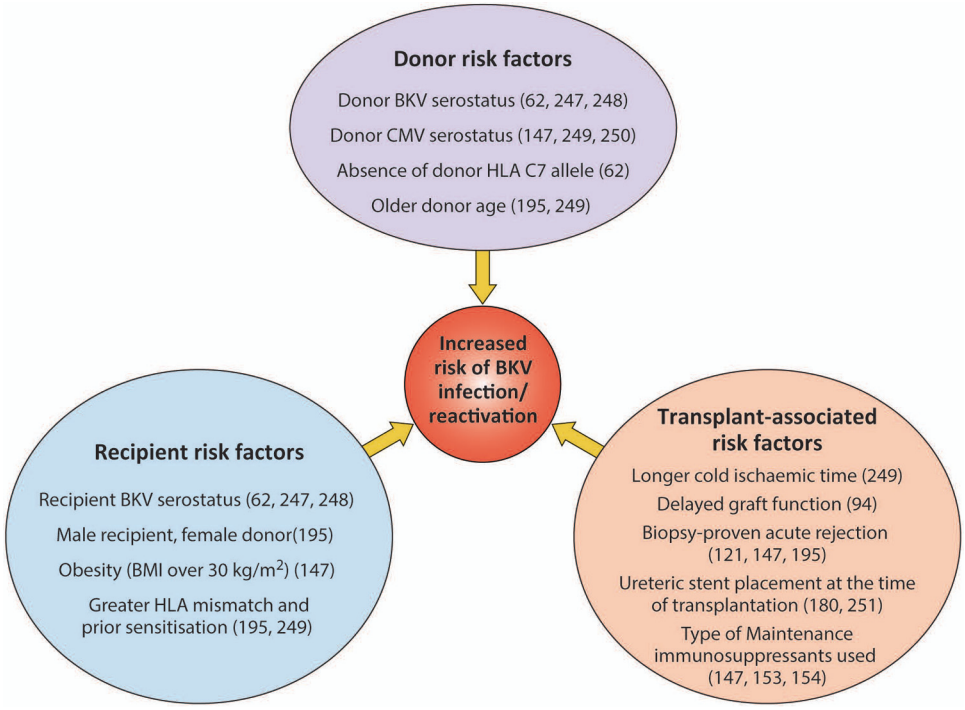

FIG 5 Identified risk factors for BKV infection and/or reactivation in transplant recipients. These risk factors are associated with either the immunological, age, sex, or metabolic status of the recipient and donor or the physiological/clinical profile of the transplanted organ. Each of these risk factors can directly or indirectly increase the risk of BKV infection and/or reactivation.

or if there is evidence of allograft dysfunction. Histologically, viral cytopathic changes affecting tubular epithelial cells are the key manifestation of BKVAN, characterized by nuclear enlargement and basophilic viral inclusions (136). Typically, there is also significant tubular cell injury and associated interstitial inflammation potentially leading to misdiagnosis of acute cellular rejection, particularly during resolution of BKVAN, when viral inclusions are less prominent (137). Persistent BKVAN eventually leads to renal parenchymal scarring with progressive tubular atrophy and interstitial fibrosis (136, 138, 139). The presence of BKV within renal tissue can be confirmed via immunohistochemistry using antibodies reactive to the large T antigen of simian virus 40 (SV40), which cross-react with BKV (140). This helps to distinguish the interstitial inflammatory changes associated with BKVAN from acute cellular rejection and is pathognomic of BKV replication within the kidney. Classification of BKVAN into three stages based on the severity of the histological findings has been proposed, since more severe changes are associated with higher BKV viral loads and poorer allograft survival (94, 138).

RISK FACTORS FOR BKV REACTIVATION

The frequencies of BKV reactivation and BKVAN after kidney transplantation vary considerably in the published literature (Table 3). Several factors have been identified that modify the risk of BKV reactivation in KTRs, although the overall degree of immunosuppression is thought to be the single largest factor promoting BKV reactivation (Fig. 5). It has been shown that both donor BKV seropositivity and recipient BKV seronegativity increase the risk of developing BKVAN and graft rejection, with a 10-fold higher risk of BK viremia in KTRs in cases where the donor was seropositive and the recipient seronegative than in cases where both were seronegative (141, 142). Recently, a number of studies also showed that not just recipient seronegativity but also the differential titers of BKV-specific antibodies are associated with the risk of viremia and viruria in KTRs (141–144). Higher anti-BKV IgG titers in donors and lower anti-BKV IgG titers in recipients increase the risk of early BK viremia (142, 143). These reports suggest

that increased vigilance for BKV in kidney donors may identify KTRs at greater risk for BKV reactivation posttransplantation. Furthermore, Verghese et al. recently showed that transplantation from donors with active BKV viruria increased the risk of BK viremia in the recipients (145).

KTRs typically receive both induction and maintenance immunosuppression. Induction agents are potent immunosuppressive medications administered early after transplantation, when the risk of acute rejection is highest (146). Maintenance immunosuppression is required indefinitely after transplantation to prevent chronic rejection and promote long-term allograft survival. Induction therapy is typically a monoclonal or polyclonal antibody that depletes host lymphocytes (thymoglobulin/ATG or alemtuzumab) or that targets CD25, the high-affinity IL-2 receptor alpha chain (basiliximab and daclizumab). Administration of antithymocyte globulin is associated with a longer duration of BK viremia as well as a higher incidence of BKVAN than those with induction with an anti-CD25 monoclonal antibody (MAb) (147–149) or no induction (121). This is consistent with the view that the major driver of BKV reactivation is immunosuppression, since lymphocyte-depleting therapy is significantly more immunosuppressive than CD25 blockade, as reflected in a much lower incidence of acute rejection (150). Similar findings were observed in the large 3C trial, which reported a significantly higher rate of BK viremia in the first 6 months following kidney transplantation for recipients randomized to alemtuzumab induction than for those receiving basiliximab (hazard ratio, 1.92 [95% confidence interval, 1.06 to 3.45]; $P = 0.03$) (151). This is in contrast to a smaller single-center retrospective series that did not identify alemtuzumab induction as a risk factor after adjustment for other potential confounders (152).

Maintenance immunosuppression for most KTRs consists of three immunosuppressive medications, typically a calcineurin inhibitor (tacrolimus or cyclosporine), an antiproliferative agent (mycophenolate or azathioprine), and a corticosteroid. Tacrolimus is associated with lower acute rejection rates than those with cyclosporine and is therefore considered a more potent immunosuppressive agent. In keeping with this, several studies suggest that tacrolimus is associated with a greater risk of BK viremia than that with cyclosporine. The DIRECT trial was a prospective open-label randomized controlled trial comparing tacrolimus to cyclosporine; all recipients received mycophenolate and corticosteroids (94). The incidence of BK viremia at 6 months posttransplantation was 16.3% in the tacrolimus arm, compared to 10.6% in the cyclosporine arm. This positive association between tacrolimus and BK viremia has been observed in other studies (95, 121, 147), as well as in U.S. registry data (148). The combination of tacrolimus, mycophenolate, and corticosteroids appears to confer a particularly high risk of BK viremia compared to that with alternative regimens (147, 153, 154), and there is also a positive correlation between greater exposure to corticosteroids and BK viremia (94, 121, 155). In contrast, BK viremia and BKVAN appear to be less common in patients receiving regimens based on mTOR inhibitors (sirolimus or everolimus), which are considered less potent immunosuppressive agents than calcineurin inhibitors (148, 156, 157). Taken together, the available data suggest that the risk of BKV reactivation is associated with the net degree of immunosuppression rather than a specific effect of particular immunosuppressive agents on BKV replication. Several other risk factors for BKV reactivation have been reported (Fig. 5). Some of these (such as episodes of acute rejection) are likely to be surrogate markers for greater exposure to immunosuppression.

THERAPEUTIC INTERVENTIONS

There are few controlled studies available to guide the management of BK viremia and BKVAN in KTRs (158). The usual clinical approach upon identification of BK viremia or BKVAN is gradual reduction of immunosuppression, guided by serial monitoring of BK viremia by PCR (149, 159–162). Typical therapeutic strategies that have been reported are discussed in Table 5. A reduction in immunosuppression risks precipitating acute rejection, which can be challenging to distinguish histologically from resolving BKVAN, as there is often persistent interstitial inflammation, while viral inclusions and

TABLE 5 Therapeutic interventions for treatment of BKV infection/disease

Therapeutic intervention	Description	Reference	Intervention strategy	No. of patients studied (no. of patients with BKVAN)	Outcome and/or comments
Reduction in immunosuppression	Reduction of immunosuppression is first-line therapy for transplant recipients with significant BKV reactivation and may lead to resolution of BK viremia or BKVAN. Typically, the dose of antiproliferative agent (mycophenolate or azathioprine) is progressively decreased, with or without a reduction in calcineurin inhibitor (CNI; tacrolimus or cyclosporine) target levels.	238	30% to 50% reduction in MMF[a] and/or CNI	28 (5)	All patients cleared BKV. Early intervention was performed immediately after the detection of BK viremia and biopsy confirmation of BKVAN.
		162	Concomitant reduction of MMF (44%) and tacrolimus (41%)	24 (16)	23/24 patients have functioning graft. Reduction in immunosuppression was performed without any antiviral therapy soon after the detection of viremia.
		149	Reduction of CNI and/or MMF to 50% or withdrawal of MMF or CNI	910 (35)	19 patients retained graft function. Withdrawal of CNI was proved to increase the survival rate.
		247	30–50% reduction in tacrolimus and/or MMF	229 (7)	Successful resolution was seen in 30 BK viremia patients and 7 BKVAN patients.
Cidofovir	Cidofovir showed successful treatment of BKV infection in patients with BKVAN or HC.	248	13 doses of cidofovir with reduced immunosuppression	75	53/75 patients cleared BKV infection.
		163	4–10 doses of cidofovir in combination with reduction or removal of tacrolimus/MMF/cyclosporine	705 (21)	9/13 patients with no adjuvant cidofovir lost their grafts. Eight patients treated with cidofovir recovered, with no side effects.
Brincidofovir	Brincidofovir is a prodrug of cidofovir and also has *in vitro* activity against BKV (249), but it appears to be less nephrotoxic than cidofovir. Case reports have described the use of brincidofovir for BKVAN.	169	Brincidofovir for 10 weeks with no reduction in immunosuppressants	20 (3)	1 patient recovered completely. This was the first report of managing BKVAN with brincidofovir.
		168	36-week course with reduced immunosuppression	1 (1)	This study is a case report on one BKVAN patient who recovered with treatment.
Leflunomide	Leflunomide has immunosuppressant and antiviral properties. In several studies, leflunomide was introduced as a substitute for the antiproliferative agent in KTRs with BKVAN (171, 174, 176). These reports suggest potential benefits, though it is hard to differentiate direct antiviral benefits of leflunomide from overall changes in immunosuppression.	250	MMF reduced to 50%, with a 60-mg dose of leflunomide	28 (5)	71% of patients cleared BKV, with 39% showing side effects.
		174	MMF was replaced by 100 mg/day of leflunomide	12 (12)	42% of patients cleared viremia, with 17% showing side effects.
Intravenous immunoglobulin (IVIG)	Pooled human immunoglobulins contain neutralizing antibodies against BKV (178) and are immunomodulatory, potentially reducing the risk of acute allograft rejection in the setting of immunosuppression reduction.	184	Reduction in immunosuppression with intravenous administration of IVIG (1 g/kg of body weight) for patients with high viral loads	53 (20)	8 patients were treated with IVIG. After 1 year, 7 patients had functioning grafts.
		180	Reduction in immunosuppression with administration of IVIG (2 g/kg)	8 (8)	88% of patients had functioning grafts.
Fluoroquinolones	Ciprofloxacin and levofloxacin have been shown to inhibit BKV replication *in vitro*; however, the clinical effectiveness of fluoroquinolones appears to be low.	194	500 mg/day of levofloxacin for 3 mo	154 (76)	Levofloxacin did not significantly reduce BKV reactivation.
		193	500 mg/day of levofloxacin for 30 days, with reduction in overall immunosuppression	39	There was no effect on BKV reactivation.
		251	500 mg/day of ciprofloxacin	43	There was no effect on BKV reactivation.
Adoptive T cell therapy	Primed BKV-reactive T cells capable of controlling BKV-associated disease are adoptively transferred to patients.	207	0.5×10^7 to 2×10^7 cells/m^2 were administered	11	Of the 7 patients with BKV reactivation, 5 achieved complete clearance, while 1 patient achieved partial clearance.
		252	2×10^7 cells/m^2 were infused	13	4 patients had a complete response, while 9 patients showed a partial response.

[a]MMF, mycophenolate mofetil.

SV40 immunohistochemistry may become negative (137). As a result, a long-term consequence of modifying immunosuppression to treat BKV-associated disease may be a higher incidence of chronic rejection, as suggested by one study reporting an excess of *de novo* donor-specific anti-HLA antibody development in recipients with persistent BK viremia (140).

Currently, there are no antiviral medications with strong evidence of clinical efficacy against BKV. Nevertheless, multiple reports have described the use of agents with potential anti-BKV activity in patients with BKVAN. In most cases, these agents have been combined with immunosuppression reduction and have been reported from uncontrolled retrospective observational studies, and therefore it is difficult to make firm conclusions about their therapeutic efficacy. Various single-center case reports and case series indicate a potential clinical benefit for cidofovir along with the reduction of immunosuppression, but no randomized trial has been reported so far (163–166). However, the clinical application of cidofovir is frequently limited by nephrotoxity. Brincidofovir (CMX001) is an orally administered prodrug of cidofovir currently undergoing phase III clinical trials and is reported to have a lower incidence of nephrotoxicity than that with cidofovir (167). Case reports have described successful outcomes for KTRs and HSCT patients with BKVAN after therapy with brincidofovir (168, 169); however, a clinical trial is needed to establish the efficacy and safety of this drug in treating BKV-associated disease.

Leflunomide, an immunosuppressant agent that also has antiviral properties against BKV *in vitro* (170), was utilized as a replacement agent in lieu of mycophenolate in several case series (171–176). These studies indicate that leflunomide is associated with a fall in BKV viral load, although it is unclear whether this reflects a reduction in overall immunosuppression or a direct antiviral effect. Leflunomide is associated with a number of significant adverse effects, including hepatitis, thrombotic microangiopathy, hemolysis, and bone marrow suppression (171). The active metabolite of leflunomide (known as teriflunomide or A771726) can be measured, and therapeutic monitoring of this has been proposed to aid in effective dosing of leflunomide, with the aim of minimizing toxicity (176). In a case series of 22 patients, achieving A771726 levels of 50 to 100 μg/ml was associated with reductions in BKV viral load during follow-up (175). Further prospective controlled studies of leflunomide are needed to confirm the efficacy and safety of this drug against BKV and associated disease (176, 177).

Intravenous immunoglobulin (IVIG) has been demonstrated to contain neutralizing antibodies against BKV (178). Several case reports and case series have described the use of IVIG as an adjunctive therapy for BKVAN (179–185); however, no controlled studies have been reported. IVIG therapy may be particularly beneficial in individuals with hypogammaglobulinemia, both with the aim of contributing passive anti-BKV immunity and also because IVIG is immunomodulatory (186) and may help to prevent allograft rejection in the context of reduced immunosuppression.

In vitro studies have demonstrated that fluoroquinolone antibiotics can inhibit BKV or SV40 polyomavirus replication *in vitro*, and fluoroquinolones have therefore been considered potential agents for controlling BKV replication (187–189). *In vitro*, the inhibitory effect of fluoroquinolones appears to be mediated via both reduction of large T antigen expression and inhibition of large T antigen helicase activity (187–189). Retrospective analysis of a trial in which a fluoroquinolone was administered as antibiotic prophylaxis at the time of kidney transplant found that fewer KTRs who received the fluoroquinolone developed BK viremia, further suggesting a possible benefit for these antibiotics in preventing BKV replication (190, 191). The combination of ciprofloxacin and leflunomide was also reported to be successful in controlling BKV replication in a single-center nonrandomized study (192). However, two subsequent prospective randomized controlled studies of levofloxacin in KTRs did not demonstrate a benefit with respect to reducing either the incidence or the level of BK viremia (193, 194). Overall, these data do not suggest that fluoroquinolones currently have a clinically significant role in the management of BKV-related disease (94).

BKV reactivation is associated with a reduction in allograft survival in KTRs. In a U.S.

registry study of over 42,000 KTRs, 3-year allograft survival was 79% for recipients who required treatment for BKV, compared to 90% for BKV-negative patients (195). A systematic review of therapy for BKV-associated complications in KTRs was published in 2010 (158). The rate of death-censored allograft loss for immunosuppression reduction alone was 8/100 patient-years, and there was no evidence that addition of leflunomide or cidofovir improved allograft survival (158). The management of BKV-associated diseases varies from center to center, and there is a need for further randomized controlled trials to define the optimal treatment strategy for KTRs with BKV reactivation.

CELLULAR IMMUNOTHERAPY

Reactivation of latent BKV is exacerbated by immunosuppression, presumably following failure of BKV-reactive T cells to control viral replication (196). Therefore, adoptive transfer of primed BKV-reactive T cells may be an effective approach to controlling BKV-associated disease. The use of T cells as a cellular therapy to restore antiviral immunity in immunocompromised patients was first demonstrated by Riddell et al. in the early 1990s (197). Over the past 2 decades, various research groups have refined the process of adoptive T cell therapy for treating various chronic virus-associated diseases (198–202). For the successful generation of virus-specific T cells, it is necessary to identify the immunogenic antigens of the virus. The immunodominant epitopes of herpesviruses, such as CMV and Epstein-Barr virus (EBV), have been well defined, enabling researchers to successfully expand CMV- or EBV-specific T cells by using synthetic viral peptides or overlapping peptide pools (203). More recently, techniques have been developed to utilize major histocompatibility complex (MHC) multimer (199, 204, 205) or IFN-γ capture technology to allow rapid selection and enrichment of virus-specific T cells (201, 206). Immunotherapeutic approaches to treat BKV-associated diseases are still in their early stages. There are very limited data about the immunodominant BKV epitopes for T cell priming. Blyth et al. recently reported the use of overlapping peptide pools derived from all five BKV antigens to expand BKV-specific human T cells (89). Functional characterization of the expanded T cell population confirmed BKV reactivity, cytokine production, and *in vitro* cytotoxicity (89). A pilot study published in 2014 reported the *in vitro* expansion of virus-reactive T cells by use of overlapping peptide pools including antigens from EBV, CMV, adenovirus, BKV, and human herpesvirus 6 (207). An alternative approach to generating virus-specific T cell products, including BKV-reactive cells, is the use of an adenoviral vector to express multiple viral proteins (208). Cell products generated using this protocol were administered to 11 HSCT recipients, either prophylactically or in response to single or multiple viral infections. Several of the study participants had active BKV replication that improved following adoptive T cell transfer, with concurrent increases in the frequency of circulating BKV-reactive T cells detected using an enzyme-linked immunosorbent spot (ELISpot) assay. None of the participants experienced significant infusion reactions or other adverse safety concerns following adoptive transfer (207). These data suggest that adoptive transfer of BKV-reactive T cells has the potential to ameliorate BKV-associated pathology and may be a significant therapeutic advance in patients with BKVAN or HC. Further investigation into the comprehensive determination of immunogenic T cell epitopes for BKV antigens and the optimization of T cell expansion protocols should aid in the development of enhanced immunotherapeutic approaches to treat BKV-associated diseases.

HEMORRHAGIC CYSTITIS

Hemorrhagic cystitis (HC) is associated with high morbidity in HSCT patients. The association of BKV with HC was first detected in the 1980s, as evidenced by the presence of high loads of BKV in the urine samples of HSCT recipients (209, 210). The frequency of BKV-associated HC in HSCT recipients is about 10%, typically at approximately 2 weeks posttransplantation (211). BKV viruria is found in about 50% of bone marrow transplant (BMT) recipients, and high levels of viruria are associated with a higher risk of developing HC (212–214). The symptoms of HC include dysuria, urinary frequency,

urinary urgency, suprapubic pain, and hematuria (211). A definitive diagnostic method for the detection of BKV-associated HC in transplant recipients has not been identified. The commonly used diagnostic approaches followed for BKV-associated diseases are listed in Table 4. While immunocompetent individuals also periodically shed BKV in urine, detection of urinary viral loads of 10^6 to 10^7 copies/ml and BK viremia of $>10^4$ copies/ml is associated with a higher risk of HC in transplant recipients (214, 215). Therapeutic approaches to treat BKV-associated HC in HSCT and BMT recipients are not well established. Approaches similar to those for the management of BKVAN have been reported for patients with HC, including modification of immunosuppressive medications and the use of cidofovir, leflunomide, and fluoroquinolone antibiotics (164, 166, 175, 216, 217).

BKV AND CANCER

BKV has been linked to various cancers, including prostate cancer and urothelial tumors (218–220), although whether BKV has a causal role in the development of cancer is controversial. It has been suggested that BKV may be oncogenic due to the expression of the early coding region-encoded proteins LTA and STA, which can initiate or drive neoplastic transformation. T antigens are known to be prooncogenic due to their ability to inactivate tumor suppressor proteins, such as p53 and pRb, leading to increased cell proliferation. Therefore, binding of the polyomavirus LTA antigen to wild-type p53 in infected cells may lead to interference with the cell cycle and increase the risk of malignant transformation (221–223). In support of this hypothesis, BKV LTA-p53 protein complexes have been detected in the cytoplasm of prostate cancer tissue (224, 225). The presence of BKV LTA-p53 complexes is not sufficient to prove that LTA is oncogenic but raises suspicion that BKV may be a risk factor for prostate cancer development. In addition, STA has been shown to increase activation of the mitogen-activated protein (MAP) kinase pathway, which may also augment cell proliferation and transformation (226).

Various studies have shown that the BKV early coding regions can induce transformation in rodent and human cells. Trabanelli et al. showed that BKV T antigens caused cellular transformation via chromosomal alteration when human fibroblasts were transfected with BKV antigens (227). However, the mechanism through which BKV antigens mediate clastogenic effects has not yet been elucidated fully. Further evidence suggesting that BKV is oncogenic comes from animal studies in which inoculation of BKV resulted in the development of tumors in rodents (27, 228). Recently, Kenan et al. showed that oncogenesis requires integration of the BKV genome into the chromosome and demonstrated a possible mechanism of BKV DNA integration and lytic infection (229). This is the only study showing integration of BKV DNA in tumor cells and needs to be confirmed.

There have been reports of a higher prevalence of BKV DNA in precancerous and early-stage cancer tissues than in healthy control tissues, possibly suggesting a "hit and run" mechanism of carcinogenesis by BKV or that BKV infection can promote the early stages of tumorigenesis (224, 225). There are also contradictory reports about the presence of BKV DNA in prostate cancer specimens (230, 231). Novel approaches are required in order to prove the role of BKV in cancer development. Whether BKV plays an important role in human cancer development remains a topic of debate.

CONCLUSIONS

BKV infection is a common childhood infection that establishes permanent latency within renal tubular and uroepithelial cells. BKV reactivation is common in immunocompromised individuals and causes significant morbidity, in particular BKVAN in KTRs and hemorrhagic cystitis in hematopoietic stem cell recipients. No specific antiviral therapy is available, and management typically consists of reducing immunosuppression with the aim of reconstituting effective BKV immune responses. BKVAN in kidney transplant recipients is associated with poorer allograft survival, due either to progressive BKV-associated damage or to rejection precipitated by a reduction in immunosup-

pression. Studies of the immune response to BKV are limited but indicate that T cells play a vital role in controlling BKV replication. There is a need for high-quality controlled clinical studies to define the optimal treatment strategies following BKV reactivation. Adoptive cell therapy using *ex vivo*-expanded BKV-reactive T cells is a novel therapeutic approach that is currently in early clinical development.

REFERENCES

1. Gardner SD, Field AM, Coleman DV, Hulme B. 1971. New human papovavirus (B.K.) isolated from urine after renal transplantation. Lancet i:1253–1257.
2. Bennett SM, Broekema NM, Imperiale MJ. 2012. BK polyomavirus: emerging pathogen. Microbes Infect 14:672–683. https://doi.org/10.1016/j.micinf.2012.02.002.
3. Chatterjee M, Weyandt TB, Frisque RJ. 2000. Identification of archetype and rearranged forms of BK virus in leukocytes from healthy individuals. J Med Virol 60:353–362.
4. Knowles WA. 2006. Discovery and epidemiology of the human polyomaviruses BK virus (BKV) and JC virus (JCV). Adv Exp Med Biol 577:19–45. https://doi.org/10.1007/0-387-32957-9_2.
5. Boukoum H, Nahdi I, Sahtout W, Skiri H, Segondy M, Aouni M. 2016. BK and JC virus infections in healthy patients compared to kidney transplant recipients in Tunisia. Microb Pathog 97:204–208. https://doi.org/10.1016/j.micpath.2016.06.015.
6. Ramos E, Drachenberg CB, Wali R, Hirsch HH. 2009. The decade of polyomavirus BK-associated nephropathy: state of affairs. Transplantation 87:621–630. https://doi.org/10.1097/TP.0b013e318197c17d.
7. van Aalderen MC, Heutinck KM, Huisman C, ten Berge IJ. 2012. BK virus infection in transplant recipients: clinical manifestations, treatment options and the immune response. Neth J Med 70:172–183.
8. Comoli P, Binggeli S, Ginevri F, Hirsch HH. 2006. Polyomavirus-associated nephropathy: update on BK virus-specific immunity. Transpl Infect Dis 8:86–94. https://doi.org/10.1111/j.1399-3062.2006.00167.x.
9. Erard V, Storer B, Corey L, Nollkamper J, Huang ML, Limaye A, Boeckh M. 2004. BK virus infection in hematopoietic stem cell transplant recipients: frequency, risk factors, and association with postengraftment hemorrhagic cystitis. Clin Infect Dis 39:1861–1865. https://doi.org/10.1086/426140.
10. Goudsmit J, Wertheim-van Dillen P, van Strien A, van der Noordaa J. 1982. The role of BK virus in acute respiratory tract disease and the presence of BKV DNA in tonsils. J Med Virol 10:91–99. https://doi.org/10.1002/jmv.1890100203.
11. Doerries K. 2006. Human polyomavirus JC and BK persistent infection. Adv Exp Med Biol 577:102–116. https://doi.org/10.1007/0-387-32957-9_8.
12. Vago L, Cinque P, Sala E, Nebuloni M, Caldarelli R, Racca S, Ferrante P, Trabottoni G, Costanzi G. 1996. JCV-DNA and BKV-DNA in the CNS tissue and CSF of AIDS patients and normal subjects. Study of 41 cases and review of the literature. J Acquir Immune Defic Syndr Hum Retrovirol 12:139–146. https://doi.org/10.1097/00042560-199606010-00006.
13. Bressollette-Bodin C, Coste-Burel M, Hourmant M, Sebille V, Andre-Garnier E, Imbert-Marcille BM. 2005. A prospective longitudinal study of BK virus infection in 104 renal transplant recipients. Am J Transplant 5:1926–1933. https://doi.org/10.1111/j.1600-6143.2005.00934.x.
14. Imperiale MJ, Major EO. 2007. Polyomaviruses, p 2263–2298. *In* Knipe DM, Howley PM, Griffin DE, Lamb RA, Martin MA, Roizman B, Straus SE (ed), Fields virology, 5th ed. Lippincott Williams & Wilkins, Philadelphia, PA.
15. Hurdiss DL, Morgan EL, Thompson RF, Prescott EL, Panou MM, Macdonald A, Ranson NA. 2016. New structural insights into the genome and minor capsid proteins of BK polyomavirus using cryo-electron microscopy. Structure 24:528–536. https://doi.org/10.1016/j.str.2016.02.008.
16. Dugan AS, Eash S, Atwood WJ. 2006. Update on BK virus entry and intracellular trafficking. Transpl Infect Dis 8:62–67. https://doi.org/10.1111/j.1399-3062.2006.00153.x.
17. Dugan AS, Eash S, Atwood WJ. 2005. An N-linked glycoprotein with alpha(2,3)-linked sialic acid is a receptor for BK virus. J Virol 79:14442–14445. https://doi.org/10.1128/JVI.79.22.14442-14445.2005.
18. Dugan AS, Gasparovic ML, Atwood WJ. 2008. Direct correlation between sialic acid binding and infection of cells by two human polyomaviruses (JC virus and BK virus). J Virol 82:2560–2564. https://doi.org/10.1128/JVI.02123-07.
19. Low JA, Magnuson B, Tsai B, Imperiale MJ. 2006. Identification of gangliosides GD1b and GT1b as receptors for BK virus. J Virol 80:1361–1366. https://doi.org/10.1128/JVI.80.3.1361-1366.2006.
20. Eash S, Querbes W, Atwood WJ. 2004. Infection of Vero cells by BK virus is dependent on caveolae. J Virol 78:11583–11590. https://doi.org/10.1128/JVI.78.21.11583-11590.2004.
21. Moriyama T, Sorokin A. 2008. Intracellular trafficking pathway of BK virus in human renal proximal tubular epithelial cells. Virology 371:336–349. https://doi.org/10.1016/j.virol.2007.09.030.
22. Jiang M, Abend JR, Tsai B, Imperiale MJ. 2009. Early events during BK virus entry and disassembly. J Virol 83:1350–1358. https://doi.org/10.1128/JVI.02169-08.
23. Nakanishi A, Itoh N, Li PP, Handa H, Liddington RC, Kasamatsu H. 2007. Minor capsid proteins of simian virus 40 are dispensable for nucleocapsid assembly and cell entry but are required for nuclear entry of the viral genome. J Virol 81:3778–3785. https://doi.org/10.1128/JVI.02664-06.
24. Nakanishi A, Li PP, Qu Q, Jafri QH, Kasamatsu H. 2007. Molecular dissection of nuclear entry-competent SV40 during infection. Virus Res 124:226–230. https://doi.org/10.1016/j.virusres.2006.10.001.
25. Nakanishi A, Shum D, Morioka H, Otsuka E, Kasamatsu H. 2002. Interaction of the Vp3 nuclear localization signal with the importin alpha 2/beta heterodimer directs nuclear entry of infecting simian virus 40. J Virol 76:9368–9377. https://doi.org/10.1128/JVI.76.18.9368-9377.2002.
26. Cubitt CL. 2006. Molecular genetics of the BK virus. Adv Exp Med Biol 577:85–95. https://doi.org/10.1007/0-387-32957-9_6.
27. Chenciner N, Meneguzzi G, Corallini A, Grossi MP, Grassi P, Barbanti-Brodano G, Milanesi G. 1980. Integrated and free viral DNA in hamster tumors induced by BK virus. Proc Natl Acad Sci U S A 77:975–979. https://doi.org/10.1073/pnas.77.2.975.
28. Pater MM, Pater A, di Mayorca G, Beth E, Giraldo G. 1982. BK virus-transformed inbred hamster brain cells: status of viral DNA in subclones. Mol Cell Biol 2:837–844. https://doi.org/10.1128/MCB.2.7.837.
29. Gorrill T, Feliciano M, Mukerjee R, Sawaya BE, Khalili K, White MK. 2006. Activation of early gene transcription in polyomavirus BK by human immunodeficiency virus type 1 Tat. J Gen Virol 87:1557–1566. https://doi.org/10.1099/vir.0.81569-0.
30. Harris KF, Christensen JB, Radany EH, Imperiale MJ. 1998. Novel mechanisms of E2F induction by BK virus large-T antigen: requirement of both the pRb-binding and the J domains. Mol Cell Biol 18:1746–1756. https://doi.org/10.1128/MCB.18.3.1746.
31. De Gascun CF, Carr MJ. 2013. Human polyomavirus reactivation: disease pathogenesis and treatment approaches. Clin Dev Immunol 2013:373579. https://doi.org/10.1155/2013/373579.
32. Carbone M, Rizzo P, Grimley PM, Procopio A, Mew DJ, Shridhar V, de Bartolomeis A, Esposito V, Giuliano MT, Steinberg SM, Levine AS, Giordano A, Pass HI. 1997. Simian virus-40 large-T antigen binds p53 in human mesotheliomas. Nat Med 3:908–912. https://doi.org/10.1038/nm0897-908.
33. Sriaroon CNGJ, Vincent A, Tucci V, Kharfan Dabaja M, Sandin R. 2010. BK virus: microbiology, epidemiology, pathogenesis, clinical manifestations and treatment. Asian Biomed 4:3–18.
34. Wang W, Simmons DT. 2009. Simian virus 40 large T antigen can specifically unwind the central palindrome at the origin of DNA replication. J Virol 83:3312–3322. https://doi.org/10.1128/JVI.01867-08.
35. Mastrangelo IA, Hough PV, Wall JS, Dodson M, Dean FB, Hurwitz J. 1989. ATP-dependent assembly of double hexamers of SV40 T antigen at the viral origin of DNA replication. Nature 338:658–662. https://doi.org/10.1038/338658a0.
36. Harris KF, Christensen JB, Imperiale MJ. 1996. BK virus large T antigen:

interactions with the retinoblastoma family of tumor suppressor proteins and effects on cellular growth control. J Virol 70:2378–2386.
37. Pipas JM. 1992. Common and unique features of T antigens encoded by the polyomavirus group. J Virol 66:3979–3985.
38. Shivakumar CV, Das GC. 1996. Interaction of human polyomavirus BK with the tumor-suppressor protein p53. Oncogene 13:323–332.
39. Cicala C, Avantaggiati ML, Graessmann A, Rundell K, Levine AS, Carbone M. 1994. Simian virus 40 small-t antigen stimulates viral DNA replication in permissive monkey cells. J Virol 68:3138–3144.
40. Howe AK, Gaillard S, Bennett JS, Rundell K. 1998. Cell cycle progression in monkey cells expressing simian virus 40 small t antigen from adenovirus vectors. J Virol 72:9637–9644.
41. Whalen B, Laffin J, Friedrich TD, Lehman JM. 1999. SV40 small T antigen enhances progression to >G2 during lytic infection. Exp Cell Res 251:121–127. https://doi.org/10.1006/excr.1999.4572.
42. Drachenberg CB, Papadimitriou JC, Wali R, Cubitt CL, Ramos E. 2003. BK polyoma virus allograft nephropathy: ultrastructural features from viral cell entry to lysis. Am J Transplant 3:1383–1392. https://doi.org/10.1046/j.1600-6135.2003.00237.x.
43. Li TC, Takeda N, Kato K, Nilsson J, Xing L, Haag L, Cheng RH, Miyamura T. 2003. Characterization of self-assembled virus-like particles of human polyomavirus BK generated by recombinant baculoviruses. Virology 311:115–124. https://doi.org/10.1016/S0042-6822(03)00141-7.
44. Jin L, Gibson PE, Booth JC, Clewley JP. 1993. Genomic typing of BK virus in clinical specimens by direct sequencing of polymerase chain reaction products. J Med Virol 41:11–17. https://doi.org/10.1002/jmv.1890410104.
45. Krumbholz A, Bininda-Emonds OR, Wutzler P, Zell R. 2008. Evolution of four BK virus subtypes. Infect Genet Evol 8:632–643. https://doi.org/10.1016/j.meegid.2008.05.006.
46. Zheng HY, Nishimoto Y, Chen Q, Hasegawa M, Zhong S, Ikegaya H, Ohno N, Sugimoto C, Takasaka T, Kitamura T, Yogo Y. 2007. Relationships between BK virus lineages and human populations. Microbes Infect 9:204–213. https://doi.org/10.1016/j.micinf.2006.11.008.
47. Ikegaya H, Saukko PJ, Tertti R, Metsarinne KP, Carr MJ, Crowley B, Sakurada K, Zheng HY, Kitamura T, Yogo Y. 2006. Identification of a genomic subgroup of BK polyomavirus spread in European populations. J Gen Virol 87:3201–3208. https://doi.org/10.1099/vir.0.82266-0.
48. Nishimoto Y, Zheng HY, Zhong S, Ikegaya H, Chen Q, Sugimoto C, Kitamura T, Yogo Y. 2007. An Asian origin for subtype IV BK virus based on phylogenetic analysis. J Mol Evol 65:103–111. https://doi.org/10.1007/s00239-006-0269-6.
49. Takasaka T, Goya N, Tokumoto T, Tanabe K, Toma H, Ogawa Y, Hokama S, Momose A, Funyu T, Fujioka T, Omori S, Akiyama H, Chen Q, Zheng HY, Ohta N, Kitamura T, Yogo Y. 2004. Subtypes of BK virus prevalent in Japan and variation in their transcriptional control region. J Gen Virol 85:2821–2827. https://doi.org/10.1099/vir.0.80363-0.
50. Jin L, Pietropaolo V, Booth JC, Ward KH, Brown DW. 1995. Prevalence and distribution of BK virus subtypes in healthy people and immunocompromised patients detected by PCR-restriction enzyme analysis. Clin Diagn Virol 3:285–295. https://doi.org/10.1016/S0928-0197(94)00044-1.
51. Yogo Y, Sugimoto C, Zhong S, Homma Y. 2009. Evolution of the BK polyomavirus: epidemiological, anthropological and clinical implications. Rev Med Virol 19:185–199. https://doi.org/10.1002/rmv.613.
52. Olsen GH, Hirsch HH, Rinaldo CH. 2009. Functional analysis of polyomavirus BK non-coding control region quasispecies from kidney transplant recipients. J Med Virol 81:1959–1967. https://doi.org/10.1002/jmv.21605.
53. Broekema NM, Imperiale MJ. 2012. Efficient propagation of archetype BK and JC polyomaviruses. Virology 422:235–241. https://doi.org/10.1016/j.virol.2011.10.026.
54. Carr MJ, McCormack GP, Mutton KJ, Crowley B. 2006. Unique BK virus non-coding control region (NCCR) variants in hematopoietic stem cell transplant recipients with and without hemorrhagic cystitis. J Med Virol 78:485–493. https://doi.org/10.1002/jmv.20566.
55. Grey F, Meyers H, White EA, Spector DH, Nelson J. 2007. A human cytomegalovirus-encoded microRNA regulates expression of multiple viral genes involved in replication. PLoS Pathog 3:e163. https://doi.org/10.1371/journal.ppat.0030163.
56. Broekema NM, Imperiale MJ. 2013. miRNA regulation of BK polyomavirus replication during early infection. Proc Natl Acad Sci U S A 110:8200–8205. https://doi.org/10.1073/pnas.1301907110.
57. Tian YC, Li YJ, Chen HC, Wu HH, Weng CH, Chen YC, Lee CC, Chang MY, Hsu HH, Yen TH, Hung CC, Yang CW. 2014. Polyomavirus BK-encoded microRNA suppresses autoregulation of viral replication. Biochem Biophys Res Commun 447:543–549. https://doi.org/10.1016/j.bbrc.2014.04.030.
58. Womer KL, Huang Y, Herren H, Dibadj K, Peng R, Murawski M, Shraybman R, Patton P, Clare-Salzler MJ, Kaplan B. 2010. Dendritic cell deficiency associated with development of BK viremia and nephropathy in renal transplant recipients. Transplantation 89:115–123. https://doi.org/10.1097/TP.0b013e3181bc6096.
59. Drake DR, III, Shawver ML, Hadley A, Butz E, Maliszewski C, Lukacher AE. 2001. Induction of polyomavirus-specific CD8(+) T lymphocytes by distinct dendritic cell subpopulations. J Virol 75:544–547. https://doi.org/10.1128/JVI.75.1.544-547.2001.
60. Drake DR, III, Moser JM, Hadley A, Altman JD, Maliszewski C, Butz E, Lukacher AE. 2000. Polyomavirus-infected dendritic cells induce antiviral CD8(+) T lymphocytes. J Virol 74:4093–4101. https://doi.org/10.1128/JVI.74.9.4093-4101.2000.
61. Gedvilaite A, Dorn DC, Sasnauskas K, Pecher G, Bulavaite A, Lawatscheck R, Staniulis J, Dalianis T, Ramqvist T, Schonrich G, Raftery MJ, Ulrich R. 2006. Virus-like particles derived from major capsid protein VP1 of different polyomaviruses differ in their ability to induce maturation in human dendritic cells. Virology 354:252–260. https://doi.org/10.1016/j.virol.2006.07.007.
62. Bohl DL, Storch GA, Ryschkewitsch C, Gaudreault-Keener M, Schnitzler MA, Major EO, Brennan DC. 2005. Donor origin of BK virus in renal transplantation and role of HLA C7 in susceptibility to sustained BK viremia. Am J Transplant 5:2213–2221. https://doi.org/10.1111/j.1600-6143.2005.01000.x.
63. Trydzenskaya H, Juerchott K, Lachmann N, Kotsch K, Kunert K, Weist B, Schonemann C, Schindler R, Nickel P, Melzig MF, Hugo C, Thomusch O, Neumann AU, Reinke P, Babel N. 2013. The genetic predisposition of natural killer cell to BK virus-associated nephropathy in renal transplant patients. Kidney Int 84:359–365. https://doi.org/10.1038/ki.2013.59.
64. Bauman Y. 2011. An identical miRNA of the human JC and BK polyoma viruses targets the stress-induced ligand ULBP3 to escape immune elimination. Cell Host Microbe 9:93–102. https://doi.org/10.1016/j.chom.2011.01.008.
65. Dugan AS, Maginnis MS, Jordan JA, Gasparovic ML, Manley K, Page R, Williams G, Porter E, O'Hara BA, Atwood WJ. 2008. Human alpha-defensins inhibit BK virus infection by aggregating virions and blocking binding to host cells. J Biol Chem 283:31125–31132. https://doi.org/10.1074/jbc.M805902200.
66. Ribeiro A, Wornle M, Motamedi N, Anders HJ, Grone EF, Nitschko H, Kurktschiev P, Debiec H, Kretzler M, Cohen CD, Grone HJ, Schlondorff D, Schmid H. 2012. Activation of innate immune defense mechanisms contributes to polyomavirus BK-associated nephropathy. Kidney Int 81:100–111. https://doi.org/10.1038/ki.2011.311.
67. Abend JR, Low JA, Imperiale MJ. 2010. Global effects of BKV infection on gene expression in human primary kidney epithelial cells. Virology 397:73–79. https://doi.org/10.1016/j.virol.2009.10.047.
68. Mannon RB, Hoffmann SC, Kampen RL, Cheng OC, Kleiner DE, Ryschkewitsch C, Curfman B, Major E, Hale DA, Kirk AD. 2005. Molecular evaluation of BK polyomavirus nephropathy. Am J Transplant 5:2883–2893. https://doi.org/10.1111/j.1600-6143.2005.01096.x.
69. Egli A, Infanti L, Dumoulin A, Buser A, Samaridis J, Stebler C, Gosert R, Hirsch HH. 2009. Prevalence of polyomavirus BK and JC infection and replication in 400 healthy blood donors. J Infect Dis 199:837–846. https://doi.org/10.1086/597126.
70. Randhawa PS, Gupta G, Vats A, Shapiro R, Viscidi RP. 2006. Immunoglobulin G, A, and M responses to BK virus in renal transplantation. Clin Vaccine Immunol 13:1057–1063. https://doi.org/10.1128/CVI.00114-06.
71. Comoli P, Cioni M, Basso S, Gagliardone C, Potenza L, Verrina E, Luppi M, Zecca M, Ghiggeri GM, Ginevri F. 2013. Immunity to polyomavirus BK infection: immune monitoring to regulate the balance between risk of BKV nephropathy and induction of alloimmunity. Clin Dev Immunol 2013:256923. https://doi.org/10.1155/2013/256923.
72. O'Donnell CD, Vogel L, Wright A, Das SR, Wrammert J, Li GM, McCausland M, Zheng NY, Yewdell JW, Ahmed R, Wilson PC, Subbarao K. 2012. Antibody pressure by a human monoclonal antibody targeting the 2009 pandemic H1N1 virus hemagglutinin drives the emergence of a virus with increased virulence in mice. mBio 3:e00120-12. https://doi.org/10.1128/mBio.00120-12.
73. Li C, Diprimio N, Bowles DE, Hirsch ML, Monahan PE, Asokan A, Rabinowitz J, Agbandje-McKenna M, Samulski RJ. 2012. Single amino acid

modification of adeno-associated virus capsid changes transduction and humoral immune profiles. J Virol 86:7752–7759. https://doi.org/10.1128/JVI.00675-12.
74. Ciarlet M, Hoshino Y, Liprandi F. 1997. Single point mutations may affect the serotype reactivity of serotype G11 porcine rotavirus strains: a widening spectrum? J Virol 71:8213–8220.
75. Pastrana DV, Ray U, Magaldi TG, Schowalter RM, Cuburu N, Buck CB. 2013. BK polyomavirus genotypes represent distinct serotypes with distinct entry tropism. J Virol 87:10105–10113. https://doi.org/10.1128/JVI.01189-13.
76. Pastrana DV, Brennan DC, Cuburu N, Storch GA, Viscidi RP, Randhawa PS, Buck CB. 2012. Neutralization serotyping of BK polyomavirus infection in kidney transplant recipients. PLoS Pathog 8:e1002650. https://doi.org/10.1371/journal.ppat.1002650.
77. Ginevri F, Azzi A, Hirsch HH, Basso S, Fontana I, Cioni M, Bodaghi S, Salotti V, Rinieri A, Botti G, Perfumo F, Locatelli F, Comoli P. 2007. Prospective monitoring of polyomavirus BK replication and impact of pre-emptive intervention in pediatric kidney recipients. Am J Transplant 7:2727–2735. https://doi.org/10.1111/j.1600-6143.2007.01984.x.
78. Schachtner T, Muller K, Stein M, Diezemann C, Sefrin A, Babel N, Reinke P. 2011. BK virus-specific immunity kinetics: a predictor of recovery from polyomavirus BK-associated nephropathy. Am J Transplant 11:2443–2452. https://doi.org/10.1111/j.1600-6143.2011.03693.x.
79. Chen Y, Trofe J, Gordon J, Du Pasquier RA, Roy-Chaudhury P, Kuroda MJ, Woodle ES, Khalili K, Koralnik IJ. 2006. Interplay of cellular and humoral immune responses against BK virus in kidney transplant recipients with polyomavirus nephropathy. J Virol 80:3495–3505. https://doi.org/10.1128/JVI.80.7.3495-3505.2006.
80. Hammer MH, Brestrich G, Andree H, Engelmann E, Rosenberger C, Tillmann H, Zwinger S, Babel N, Nickel P, Volk HD, Reinke P. 2006. HLA type-independent method to monitor polyoma BK virus-specific CD4 and CD8 T-cell immunity. Am J Transplant 6:625–631. https://doi.org/10.1111/j.1600-6143.2005.01221.x.
81. Binggeli S, Egli A, Schaub S, Binet I, Mayr M, Steiger J, Hirsch HH. 2007. Polyomavirus BK-specific cellular immune response to VP1 and large T-antigen in kidney transplant recipients. Am J Transplant 7:1131–1139. https://doi.org/10.1111/j.1600-6143.2007.01754.x.
82. Renner FC, Dietrich H, Bulut N, Celik D, Freitag E, Gaertner N, Karoui S, Mark J, Raatz C, Weimer R, Feustel A. 2013. The risk of polyomavirus-associated graft nephropathy is increased by a combined suppression of CD8 and CD4 cell-dependent immune effects. Transplant Proc 45:1608–1610. https://doi.org/10.1016/j.transproceed.2013.01.026.
83. Schaenman JM, Korin Y, Sidwell T, Kandarian F, Harre N, Gjertson D, Lum EL, Reddy U, Huang E, Pham PT, Bunnapradist S, Danovitch GM, Veale J, Gritsch HA, Reed EF. 7 July 2016. Increased frequency of BK virus-specific polyfunctional CD8+ T cells predict successful control of BK viremia after kidney transplantation. Transplantation https://doi.org/10.1097/tp.0000000000001314.
84. Walker S, Fazou C, Crough T, Holdsworth R, Kiely P, Veale M, Bell S, Gailbraith A, McNeil K, Jones S, Khanna R. 2007. Ex vivo monitoring of human cytomegalovirus-specific CD8+ T-cell responses using QuantiFERON-CMV. Transpl Infect Dis 9:165–170. https://doi.org/10.1111/j.1399-3062.2006.00199.x.
85. Randhawa PS, Popescu I, Macedo C, Zeevi A, Shapiro R, Vats AN, Metes D. 2006. Detection of CD8+ T cells sensitized to BK virus large T antigen in healthy volunteers and kidney transplant recipients. Hum Immunol 67:298–302. https://doi.org/10.1016/j.humimm.2006.02.031.
86. Schneidawind D, Schmitt A, Wiesneth M, Mertens T, Bunjes D, Freund M, Schmitt M. 2010. Polyomavirus BK-specific CD8+ T cell responses in patients after allogeneic stem cell transplant. Leuk Lymphoma 51:1055–1062. https://doi.org/10.3109/10428191003746323.
87. Mueller K, Schachtner T, Sattler A, Meier S, Friedrich P, Trydzenskaya H, Hinrichs C, Trappe R, Thiel A, Reinke P, Babel N. 2011. BK-VP3 as a new target of cellular immunity in BK virus infection. Transplantation 91:100–107. https://doi.org/10.1097/TP.0b013e3181fe1335.
88. Zhou W, Sharma M, Martinez J, Srivastava T, Diamond DJ, Knowles W, Lacey SF. 2007. Functional characterization of BK virus-specific CD4+ T cells with cytotoxic potential in seropositive adults. Viral Immunol 20:379–388. https://doi.org/10.1089/vim.2007.0030.
89. Blyth E, Clancy L, Simms R, Gaundar S, O'Connell P, Micklethwaite K, Gottlieb DJ. 2011. BK virus-specific T cells for use in cellular therapy show specificity to multiple antigens and polyfunctional cytokine responses. Transplantation 92:1077–1084. https://doi.org/10.1097/TP.0b013e31823328c0.
90. Krymskaya L, Sharma MC, Martinez J, Haq W, Huang EC, Limaye AP, Diamond DJ, Lacey SF. 2005. Cross-reactivity of T lymphocytes recognizing a human cytotoxic T-lymphocyte epitope within BK and JC virus VP1 polypeptides. J Virol 79:11170–11178. https://doi.org/10.1128/JVI.79.17.11170-11178.2005.
91. Trydzenskaya H, Sattler A, Muller K, Schachtner T, Dang-Heine C, Friedrich P, Nickel P, Hoerstrup J, Schindler R, Thiel A, Melzig MF, Reinke P, Babel N. 2011. Novel approach for improved assessment of phenotypic and functional characteristics of BKV-specific T-cell immunity. Transplantation 92:1269–1277. https://doi.org/10.1097/TP.0b013e318234e0e5.
92. Weist BJ, Schmueck M, Fuehrer H, Sattler A, Reinke P, Babel N. 2014. The role of CD4(+) T cells in BKV-specific T cell immunity. Med Microbiol Immunol 203:395–408. https://doi.org/10.1007/s00430-014-0348-z.
93. Weist BJ, Wehler P, El Ahmad L, Schmueck-Henneresse M, Millward JM, Nienen M, Neumann AU, Reinke P, Babel N. 2015. A revised strategy for monitoring BKV-specific cellular immunity in kidney transplant patients. Kidney Int 88:1293–1303. https://doi.org/10.1038/ki.2015.215.
94. Hirsch HH, Randhawa P, AST Infectious Diseases Community of Practice. 2013. BK polyomavirus in solid organ transplantation. Am J Transplant 13(Suppl 4):S179–S188. https://doi.org/10.1111/ajt.12110.
95. Hirsch HH, Vincenti F, Friman S, Tuncer M, Citterio F, Wiecek A, Scheuermann EH, Klinger M, Russ G, Pescovitz MD, Prestele H. 2013. Polyomavirus BK replication in de novo kidney transplant patients receiving tacrolimus or cyclosporine: a prospective, randomized, multicenter study. Am J Transplant 13:136–145. https://doi.org/10.1111/j.1600-6143.2012.04320.x.
96. Zeng G, Huang Y, Huang Y, Lyu Z, Lesniak D, Randhawa P. 2016. Antigen-specificity of T cell infiltrates in biopsies with T cell-mediated rejection and BK polyomavirus viremia: analysis by next generation sequencing. Am J Transplant 16:3131–3138. https://doi.org/10.1111/ajt.13911.
97. Mutlu E, Koksoy S, Mutlu D, Yilmaz VT, Kocak H, Dinckan A, Suleymanlar G, Gultekin M. 2015. Quantitative analysis of BKV-specific CD4+ T cells before and after kidney transplantation. Transpl Immunol 33:20–26. https://doi.org/10.1016/j.trim.2015.05.005.
98. Sharma MC, Zhou W, Martinez J, Krymskaya L, Srivastava T, Haq W, Diamond DJ, Lacey SF. 2006. Cross-reactive CTL recognizing two HLA-A*02-restricted epitopes within the BK virus and JC virus VP1 polypeptides are frequent in immunocompetent individuals. Virology 350:128–136. https://doi.org/10.1016/j.virol.2006.02.040.
99. Chen Y, Trofe J, Gordon J, Autissier P, Woodle ES, Koralnik IJ. 2008. BKV and JCV large T antigen-specific CD8+ T cell response in HLA A*0201+ kidney transplant recipients with polyomavirus nephropathy and patients with progressive multifocal leukoencephalopathy. J Clin Virol 42:198–202. https://doi.org/10.1016/j.jcv.2008.01.005.
100. Tagaram HR, Watson AM, Lemonnier FA, Staveley-O'Carroll K, Tevethia SS, Schell TD. 2008. An SV40 VP1-derived epitope recognized by CD8+ T cells is naturally processed and presented by HLA-A*0201 and cross-reactive with human polyomavirus determinants. Virology 376:183–190. https://doi.org/10.1016/j.virol.2008.02.033.
101. Li J, Melenhorst J, Hensel N, Rezvani K, Sconocchia G, Kilical Y, Hou J, Curfman B, Major E, Barrett AJ. 2006. T-cell responses to peptide fragments of the BK virus T antigen: implications for cross-reactivity of immune response to JC virus. J Gen Virol 87:2951–2960. https://doi.org/10.1099/vir.0.82094-0.
102. van Aalderen MC, Remmerswaal EB, Heutinck KM, ten Brinke A, Pircher H, van Lier RA, ten Berge IJ. 2013. Phenotypic and functional characterization of circulating polyomavirus BK VP1-specific CD8+ T cells in healthy adults. J Virol 87:10263–10272. https://doi.org/10.1128/JVI.01540-13.
103. Provenzano M, Bracci L, Wyler S, Hudolin T, Sais G, Gosert R, Zajac P, Palu G, Heberer M, Hirsch HH, Spagnoli GC. 2006. Characterization of highly frequent epitope-specific CD45RA+/CCR7+/− T lymphocyte responses against p53-binding domains of the human polyomavirus BK large tumor antigen in HLA-A*0201+ BKV-seropositive donors. J Transl Med 4:47. https://doi.org/10.1186/1479-5876-4-47.
104. Ramaswami B, Popescu I, Macedo C, Metes D, Bueno M, Zeevi A, Shapiro R, Viscidi R, Randhawa PS. 2009. HLA-A01-, -A03-, and -A024-binding nanomeric epitopes in polyomavirus BK large T antigen. Hum Immunol 70:722–728. https://doi.org/10.1016/j.humimm.2009.05.003.
105. Cioni M, Leboeuf C, Comoli P, Ginevri F, Hirsch HH. 2016. Characterization of immunodominant BK polyomavirus 9mer epitope T cell re-

sponses. Am J Transplant 16:1193–1206. https://doi.org/10.1111/ajt.13598.
106. Sahoo MK, Tan SK, Chen SF, Kapusinszky B, Concepcion KR, Kjelson L, Mallempati K, Farina HM, Fernandez-Vina M, Tyan D, Grimm PC, Anderson MW, Concepcion W, Pinsky BA. 2015. Limited variation in BK virus T-cell epitopes revealed by next-generation sequencing. J Clin Microbiol 53:3226–3233. https://doi.org/10.1128/JCM.01385-15.
107. Akazawa Y, Terada Y, Yamane T, Tanaka S, Aimoto M, Koh H, Nakane T, Koh KR, Nakamae H, Ohsawa M, Wakasa K, Hino M. 2012. Fatal BK virus pneumonia following stem cell transplantation. Transpl Infect Dis 14:E142–E146. https://doi.org/10.1111/tid.12011.
108. Vidal JE, Fink MC, Cedeno-Laurent F, Delbue S, Ferrante P, Dauar RF, Filho FB, Nogueira RS, Calore EE, Pannuti CS, Trujillo JR, de Oliveira AC. 2007. BK virus associated meningoencephalitis in an AIDS patient treated with HAART. AIDS Res Ther 4:13. https://doi.org/10.1186/1742-6405-4-13.
109. Behre G, Becker M, Christopeit M. 2008. BK virus encephalitis in an allogeneic hematopoietic stem cell recipient. Bone Marrow Transplant 42:499. https://doi.org/10.1038/bmt.2008.198.
110. Lopes da Silva R, Ferreira I, Teixeira G, Cordeiro D, Mafra M, Costa I, Bravo Marques JM, Abecasis M. 2011. BK virus encephalitis with thrombotic microangiopathy in an allogeneic hematopoietic stem cell transplant recipient. Transpl Infect Dis 13:161–167. https://doi.org/10.1111/j.1399-3062.2010.00581.x.
111. Daveson KL, Ong CW, Bowden S, Koina ME, Hallam LA. 2013. BK virus-associated progressive multifocal leukoencephalopathy. Med J Aust 198:216–218. https://doi.org/10.5694/mja12.10072.
112. Bakri FG, Bahou YG, Al-Sammarrai FA, Hadidy A, Gharaibeh A, Zaid GK, Mahafzah A, Samara OA, Ababneh NA, Zak I. 2013. Fatal encephalitis due to BK virus in a patient with common variable immunodeficiency: a case report. J Clin Virol 57:363–369. https://doi.org/10.1016/j.jcv.2013.04.016.
113. Lee SY, Lee SR, Kim DS, Choi CW, Kim BS, Park Y. 2013. BK virus encephalitis without concurrent hemorrhagic cystitis in an allogeneic hematopoietic stem cell transplant recipient. Blood Res 48:226–228. https://doi.org/10.5045/br.2013.48.3.226.
114. Chittick P, Williamson JC, Ohl CA. 2013. BK virus encephalitis: case report, review of the literature, and description of a novel treatment modality. Ann Pharmacother 47:1229–1233. https://doi.org/10.1177/1060028013500646.
115. Jun JB, Choi Y, Kim H, Lee SH, Jeong J, Jung J. 2016. BK polyomavirus encephalitis in a patient with thrombotic microangiopathy after an allogeneic hematopoietic stem cell transplant. Transpl Infect Dis 18:950–953. https://doi.org/10.1111/tid.12620.
116. Galan A, Rauch CA, Otis CN. 2005. Fatal BK polyoma viral pneumonia associated with immunosuppression. Hum Pathol 36:1031–1034. https://doi.org/10.1016/j.humpath.2005.07.001.
117. Pavsic J, Devonshire AS, Parkes H, Schimmel H, Foy CA, Karczmarczyk M, Gutierrez-Aguirre I, Honeyborne I, Huggett JF, McHugh TD, Milavec M, Zeichhardt H, Zel J. 2015. Standardization of nucleic acid tests for clinical measurements of bacteria and viruses. J Clin Microbiol 53:2008–2014. https://doi.org/10.1128/JCM.02136-14.
118. Nickeleit V, Klimkait T, Binet IF, Dalquen P, Del Zenero V, Thiel G, Mihatsch MJ, Hirsch HH. 2000. Testing for polyomavirus type BK DNA in plasma to identify renal-allograft recipients with viral nephropathy. N Engl J Med 342:1309–1315. https://doi.org/10.1056/NEJM200005043421802.
119. Randhawa P, Ho A, Shapiro R, Vats A, Swalsky P, Finkelstein S, Uhrmacher J, Weck K. 2004. Correlates of quantitative measurement of BK polyomavirus (BKV) DNA with clinical course of BKV infection in renal transplant patients. J Clin Microbiol 42:1176–1180. https://doi.org/10.1128/JCM.42.3.1176-1180.2004.
120. Viscount HB, Eid AJ, Espy MJ, Griffin MD, Thomsen KM, Harmsen WS, Razonable RR, Smith TF. 2007. Polyomavirus polymerase chain reaction as a surrogate marker of polyomavirus-associated nephropathy. Transplantation 84:340–345. https://doi.org/10.1097/01.tp.0000275205.41078.51.
121. Hirsch HH, Knowles W, Dickenmann M, Passweg J, Klimkait T, Mihatsch MJ, Steiger J. 2002. Prospective study of polyomavirus type BK replication and nephropathy in renal-transplant recipients. N Engl J Med 347:488–496. https://doi.org/10.1056/NEJMoa020439.
122. Govind S, Hockley J, Morris C, Collaborative Study Group. 2015. Collaborative study to establish the 1st WHO international standard for BKV DNA for nucleic acid amplification technique (NAT)-based assays. WHO/BS/2015.2270. WHO, Geneva, Switzerland.
123. Ding R, Medeiros M, Dadhania D, Muthukumar T, Kracker D, Kong JM, Epstein SR, Sharma VK, Seshan SV, Li B, Suthanthiran M. 2002. Noninvasive diagnosis of BK virus nephritis by measurement of messenger RNA for BK virus VP1 in urine. Transplantation 74:987–994. https://doi.org/10.1097/00007890-200210150-00016.
124. Dadhania D, Snopkowski C, Ding R, Muthukumar T, Lee J, Bang H, Sharma VK, Seshan S, August P, Kapur S, Suthanthiran M. 2010. Validation of noninvasive diagnosis of BK virus nephropathy and identification of prognostic biomarkers. Transplantation 90:189–197. https://doi.org/10.1097/TP.0b013e3181e2a932.
125. Singh HK, Reisner H, Derebail VK, Kozlowski T, Nickeleit V. 2015. Polyomavirus nephropathy: quantitative urinary polyomavirus-Haufen testing accurately predicts the degree of intrarenal viral disease. Transplantation 99:609–615. https://doi.org/10.1097/TP.0000000000000367.
126. Singh HK, Andreoni KA, Madden V, True K, Detwiler R, Weck K, Nickeleit V. 2009. Presence of urinary Haufen accurately predicts polyomavirus nephropathy. J Am Soc Nephrol 20:416–427. https://doi.org/10.1681/ASN.2008010117.
127. Viswesh V, Yost SE, Kaplan B. 2015. The prevalence and implications of BK virus replication in non-renal solid organ transplant recipients: a systematic review. Transplant Rev (Orlando) 29:175–180. https://doi.org/10.1016/j.trre.2015.02.004.
128. Kuppachi S, Kaur D, Holanda DG, Thomas CP. 2016. BK polyoma virus infection and renal disease in non-renal solid organ transplantation. Clin Kidney J 9:310–318. https://doi.org/10.1093/ckj/sfv143.
129. Brennan DC, Agha I, Bohl DL, Schnitzler MA, Hardinger KL, Lockwood M, Torrence S, Schuessler R, Roby T, Gaudreault-Keener M, Storch GA. 2005. Incidence of BK with tacrolimus versus cyclosporine and impact of preemptive immunosuppression reduction. Am J Transplant 5:582–594. https://doi.org/10.1111/j.1600-6143.2005.00742.x.
130. Kuypers DR. 2012. Management of polyomavirus-associated nephropathy in renal transplant recipients. Nat Rev Nephrol 8:390–402. https://doi.org/10.1038/nrneph.2012.64.
131. Wiseman AC. 2009. Polyomavirus nephropathy: a current perspective and clinical considerations. Am J Kidney Dis 54:131–142. https://doi.org/10.1053/j.ajkd.2009.01.271.
132. Timpone JG, Jr, Kumar PN. 2013. Infectious Disease Clinics of North America. Infectious disease challenges in solid organ transplant recipients. Preface. Infect Dis Clin North Am 27:xi–xiii. https://doi.org/10.1016/j.idc.2013.03.001.
133. Hodowanec AC, Simon DM. 2015. BK virus screening and management practices among US renal transplant programs: a survey. Transpl Int 28:1339–1341. https://doi.org/10.1111/tri.12602.
134. Chakera A, Dyar OJ, Hughes E, Bennett S, Hughes D, Roberts IS. 2011. Detection of polyomavirus BK reactivation after renal transplantation using an intensive decoy cell surveillance program is cost-effective. Transplantation 92:1018–1023. https://doi.org/10.1097/TP.0b013e318230c09b.
135. Bennett WM, Meyer L, Ridenour J, Batiuk TD. 2010. Surveillance and modification of immunosuppression minimizes BK virus nephropathy. Am J Nephrol 32:10–12. https://doi.org/10.1159/000313888.
136. Drachenberg CB, Hirsch HH, Ramos E, Papadimitriou JC. 2005. Polyomavirus disease in renal transplantation: review of pathological findings and diagnostic methods. Hum Pathol 36:1245–1255. https://doi.org/10.1016/j.humpath.2005.08.009.
137. Menter T, Mayr M, Schaub S, Mihatsch MJ, Hirsch HH, Hopfer H. 2013. Pathology of resolving polyomavirus-associated nephropathy. Am J Transplant 13:1474–1483. https://doi.org/10.1111/ajt.12218.
138. Drachenberg CB, Papadimitriou JC, Hirsch HH, Wali R, Crowder C, Nogueira J, Cangro CB, Mendley S, Mian A, Ramos E. 2004. Histological patterns of polyomavirus nephropathy: correlation with graft outcome and viral load. Am J Transplant 4:2082–2092. https://doi.org/10.1046/j.1600-6143.2004.00603.x.
139. Nickeleit V, Hirsch HH, Binet IF, Gudat F, Prince O, Dalquen P, Thiel G, Mihatsch MJ. 1999. Polyomavirus infection of renal allograft recipients: from latent infection to manifest disease. J Am Soc Nephrol 10:1080–1089.
140. Sawinski D, Goral S. 2015. BK virus infection: an update on diagnosis and treatment. Nephrol Dial Transplant 30:209–217. https://doi.org/10.1093/ndt/gfu023.
141. Sood P, Senanayake S, Sujeet K, Medipalli R, Van-Why SK, Cronin DC, Johnson CP, Hariharan S. 2013. Donor and recipient BKV-specific IgG antibody and posttransplantation BKV infection: a prospective single-

center study. Transplantation 95:896–902. https://doi.org/10.1097/TP.0b013e318282ba83.
142. Wunderink HF, van der Meijden E, van der Blij-de Brouwer CS, Mallat MJ, Haasnoot GW, van Zwet EW, Claas EC, de Fijter JW, Kroes AC, Arnold F, Touze A, Claas FH, Rotmans JI, Feltkamp MC. 2017. Pretransplantation donor-recipient pair seroreactivity against BK polyomavirus predicts viremia and nephropathy after kidney transplantation. Am J Transplant 17:161–172. https://doi.org/10.1111/ajt.13880.
143. Ali AM, Gibson IW, Birk P, Blydt-Hansen TD. 2011. Pretransplant serologic testing to identify the risk of polyoma BK viremia in pediatric kidney transplant recipients. Pediatr Transplant 15:827–834. https://doi.org/10.1111/j.1399-3046.2011.01583.x.
144. Bohl DL, Brennan DC, Ryschkewitsch C, Gaudreault-Keener M, Major EO, Storch GA. 2008. BK virus antibody titers and intensity of infections after renal transplantation. J Clin Virol 43:184–189. https://doi.org/10.1016/j.jcv.2008.06.009.
145. Verghese PS, Schmeling DO, Knight JA, Matas AJ, Balfour HH. 2015. The impact of donor viral replication at transplant on recipient infections posttransplant: a prospective study. Transplantation 99:602–608. https://doi.org/10.1097/TP.0000000000000354.
146. Ghanta M, Dreier J, Jacob R, Lee I. 2013. Overview of immunosuppression in renal transplantation. *In* Rath T (ed), Current issues and future direction in kidney transplantation. InTech, Rijeka, Croatia. https://doi.org/10.5772/54865.
147. Borni-Duval C, Caillard S, Olagne J, Perrin P, Braun-Parvez L, Heibel F, Moulin B. 2013. Risk factors for BK virus infection in the era of therapeutic drug monitoring. Transplantation 95:1498–1505. https://doi.org/10.1097/TP.0b013e3182921995.
148. Dharnidharka VR, Cherikh WS, Abbott KC. 2009. An OPTN analysis of national registry data on treatment of BK virus allograft nephropathy in the United States. Transplantation 87:1019–1026. https://doi.org/10.1097/TP.0b013e31819cc383.
149. Weiss AS, Gralla J, Chan L, Klem P, Wiseman AC. 2008. Aggressive immunosuppression minimization reduces graft loss following diagnosis of BK virus-associated nephropathy: a comparison of two reduction strategies. Clin J Am Soc Nephrol 3:1812–1819. https://doi.org/10.2215/CJN.05691207.
150. Brennan DC, Daller JA, Lake KD, Cibrik D, Del Castillo D, Thymoglobulin Induction Study Group. 2006. Rabbit antithymocyte globulin versus basiliximab in renal transplantation. N Engl J Med 355:1967–1977. https://doi.org/10.1056/NEJMoa060068.
151. 3C Study Collaborative Group, Haynes R, Harden P, Judge P, Blackwell L, Emberson J, Landray MJ, Baigent C, Friend PJ. 2014. Alemtuzumab-based induction treatment versus basiliximab-based induction treatment in kidney transplantation (the 3C Study): a randomised trial. Lancet 384:1684–1690. https://doi.org/10.1016/S0140-6736(14)61095-3.
152. Theodoropoulos NWE, Penugonda S, Ladner DP, Stosor V, Leventhal J, Friedewald J, Angarone MP, Ison MG. 2013. BK virus replication and nephropathy after alemtuzumab-induced kidney transplantation. Am J Transplant 13:197–206. https://doi.org/10.1111/j.1600-6143.2012.04314.x.
153. Drachenberg CB, Hirsch HH, Papadimitriou JC, Gosert R, Wali RK, Munivenkatappa R, Nogueira J, Cangro CB, Haririan A, Mendley S, Ramos E. 2007. Polyomavirus BK versus JC replication and nephropathy in renal transplant recipients: a prospective evaluation. Transplantation 84:323–330. https://doi.org/10.1097/01.tp.0000269706.59977.a5.
154. Mengel M, Marwedel M, Radermacher J, Eden G, Schwarz A, Haller H, Kreipe H. 2003. Incidence of polyomavirus-nephropathy in renal allografts: influence of modern immunosuppressive drugs. Nephrol Dial Transplant 18:1190–1196. https://doi.org/10.1093/ndt/gfg072.
155. Basse GMC, Kamar N, Guitard J, Ribes D, Esposito L, Rostaing L. 2007. Prospective evaluation of BK virus DNAemia in renal transplant patients and their transplant outcome. Transplant Proc 39:84–87. https://doi.org/10.1016/j.transproceed.2006.11.001.
156. Benavides CA, Pollard VB, Mauiyyedi S, Podder H, Knight R, Kahan BD. 2007. BK virus-associated nephropathy in sirolimus-treated renal transplant patients: incidence, course, and clinical outcomes. Transplantation 84:83–88. https://doi.org/10.1097/01.tp.0000268524.27506.39.
157. Moscarelli LCL, Antognoli G, Zanazzi M, Di Maria L, Carta P, Minetti E. 2013. Everolimus leads to a lower risk of BKV viremia than mycophenolic acid in de novo renal transplantation patients: a single-center experience. Clin Transplant 27:546–554. https://doi.org/10.1111/ctr.12151.
158. Johnston O, Jaswal D, Gill JS, Doucette S, Fergusson DA, Knoll GA. 2010. Treatment of polyomavirus infection in kidney transplant recipients: a systematic review. Transplantation 89:1057–1070. https://doi.org/10.1097/TP.0b013e3181d0e15e.
159. Almeras C, Vetromile F, Garrigue V, Szwarc I, Foulongne V, Mourad G. 2011. Monthly screening for BK viremia is an effective strategy to prevent BK virus nephropathy in renal transplant recipients. Transpl Infect Dis 13:101–108. https://doi.org/10.1111/j.1399-3062.2011.00619.x.
160. Alméras C, Foulongne V, Garrigue V, Szwarc I, Vetromile F, Segondy M, Mourad G. 2008. Does reduction in immunosuppression in viremic patients prevent BK virus nephropathy in de novo renal transplant recipients? A prospective study. Transplantation 85:1099–1104. https://doi.org/10.1097/TP.0b013e31816a33d4.
161. Hardinger KL, Koch MJ, Bohl DJ, Storch GA, Brennan DC. 2010. BK-virus and the impact of pre-emptive immunosuppression reduction: 5-year results. Am J Transplant 10:407–415. https://doi.org/10.1111/j.1600-6143.2009.02952.x.
162. Schaub S, Hirsch HH, Dickenmann M, Steiger J, Mihatsch MJ, Hopfer H, Mayr M. 2010. Reducing immunosuppression preserves allograft function in presumptive and definitive polyomavirus-associated nephropathy. Am J Transplant 10:2615–2623. https://doi.org/10.1111/j.1600-6143.2010.03310.x.
163. Kuypers DR, Vandooren AK, Lerut E, Evenepoel P, Claes K, Snoeck R, Naesens L, Vanrenterghem Y. 2005. Adjuvant low-dose cidofovir therapy for BK polyomavirus interstitial nephritis in renal transplant recipients. Am J Transplant 5:1997–2004. https://doi.org/10.1111/j.1600-6143.2005.00980.x.
164. Kwon HJ, Kang JH, Lee JW, Chung NG, Kim HK, Cho B. 2013. Treatment of BK virus-associated hemorrhagic cystitis in pediatric hematopoietic stem cell transplant recipients with cidofovir: a single-center experience. Transpl Infect Dis 15:569–574. https://doi.org/10.1111/tid.12136.
165. Muller WJ, Levin MJ, Shin YK, Robinson C, Quinones R, Malcolm J, Hild E, Gao D, Giller R. 2005. Clinical and in vitro evaluation of cidofovir for treatment of adenovirus infection in pediatric hematopoietic stem cell transplant recipients. Clin Infect Dis 41:1812–1816. https://doi.org/10.1086/498151.
166. Savona MR, Newton D, Frame D, Levine JE, Mineishi S, Kaul DR. 2007. Low-dose cidofovir treatment of BK virus-associated hemorrhagic cystitis in recipients of hematopoietic stem cell transplant. Bone Marrow Transplant 39:783–787. https://doi.org/10.1038/sj.bmt.1705678.
167. Marty FM, Winston DJ, Rowley SD, Vance E, Papanicolaou GA, Mullane KM, Brundage TM, Robertson AT, Godkin S, Mommeja-Marin H, Boeckh M, CMX001-201 Clinical Study Group. 2013. CMX001 to prevent cytomegalovirus disease in hematopoietic-cell transplantation. N Engl J Med 369:1227–1236. https://doi.org/10.1056/NEJMoa1303688.
168. Reisman L, Habib S, McClure GB, Latiolais LS, Vanchiere JA. 2014. Treatment of BK virus-associated nephropathy with CMX001 after kidney transplantation in a young child. Pediatr Transplant 18:E227–E231. https://doi.org/10.1111/petr.12340.
169. Papanicolaou GA, Lee YJ, Young JW, Seshan SV, Boruchov AM, Chittick G, Mommeja-Marin H, Glezerman IG. 2015. Brincidofovir for polyomavirus-associated nephropathy after allogeneic hematopoietic stem cell transplantation. Am J Kidney Dis 65:780–784. https://doi.org/10.1053/j.ajkd.2014.11.020.
170. Liacini A, Seamone ME, Muruve DA, Tibbles LA. 2010. Anti-BK virus mechanisms of sirolimus and leflunomide alone and in combination: toward a new therapy for BK virus infection. Transplantation 90:1450–1457. https://doi.org/10.1097/TP.0b013e3182007be2.
171. Williams JW, Javaid B, Kadambi PV, Gillen D, Harland R, Thistlewaite JR, Garfinkel M, Foster P, Atwood W, Millis JM, Meehan SM, Josephson MA. 2005. Leflunomide for polyomavirus type BK nephropathy. N Engl J Med 352:1157–1158. https://doi.org/10.1056/NEJM200503173521125.
172. Teschner S, Gerke P, Geyer M, Wilpert J, Krumme B, Benzing T, Walz G. 2009. Leflunomide therapy for polyomavirus-induced allograft nephropathy: efficient BK virus elimination without increased risk of rejection. Transplant Proc 41:2533–2538. https://doi.org/10.1016/j.transproceed.2009.06.099.
173. Wu JK, Harris MT. 2008. Use of leflunomide in the treatment of polyomavirus BK-associated nephropathy. Ann Pharmacother 42:1679–1685. https://doi.org/10.1345/aph.1L180.
174. Faguer SHH, Kamar N, Guilbeau-Frugier C, Ribes D, Guitard J, Esposito L, Cointault O, Modesto A, Lavit M, Mengelle C, Rostaing L. 2007. Leflunomide treatment for polyomavirus BK-associated nephropathy

after kidney transplantation. Transplant Int 20:962–969. https://doi.org/10.1111/j.1432-2277.2007.00523.x.
175. Josephson MA, Gillen D, Javaid B, Kadambi P, Meehan S, Foster P, Harland R, Thistlethwaite RJ, Garfinkel M, Atwood W, Jordan J, Sadhu M, Millis MJ, Williams J. 2006. Treatment of renal allograft polyoma BK virus infection with leflunomide. Transplantation 81:704–710. https://doi.org/10.1097/01.tp.0000181149.76113.50.
176. Krisl JC, Taber DJ, Pilch N, Chavin K, Bratton C, Thomas B, McGillicuddy J, Baliga P. 2012. Leflunomide efficacy and pharmacodynamics for the treatment of BK viral infection. Clin J Am Soc Nephrol 7:1003–1009. https://doi.org/10.2215/CJN.12531211.
177. Cuellar-Rodriguez J, Stephany B, Poggio E, Mossad SB, Goldfarb D, Lard M, Askar M, Fatica R, Srinivas T, Braun W, Shoskes D, Flechner S, Schmitt SK, Shrestha R, Avery RK. 2013. Contrasting patterns of viral load response in transplant recipients with BK polyomavirus DNAemia on leflunomide therapy. Clin Transplant 27:E230–E236. https://doi.org/10.1111/ctr.12110.
178. Randhawa P, Pastrana DV, Zeng G, Huang Y, Shapiro R, Sood P, Puttarajappa C, Berger M, Hariharan S, Buck CB. 2015. Commercially available immunoglobulins contain virus neutralizing antibodies against all major genotypes of polyomavirus BK. Am J Transplant 15:1014–1020. https://doi.org/10.1111/ajt.13083.
179. Randhawa PS, Schonder K, Shapiro R, Farasati N, Huang Y. 2010. Polyomavirus BK neutralizing activity in human immunoglobulin preparations. Transplantation 89:1462–1465. https://doi.org/10.1097/TP.0b013e3181daaaf1.
180. Sener A, House AA, Jevnikar AM, Boudville N, McAlister VC, Muirhead N, Rehman F, Luke PPW. 2006. Intravenous immunoglobulin as a treatment for BK virus associated nephropathy: one-year follow-up of renal allograft recipients. Transplantation 81:117–120. https://doi.org/10.1097/01.tp.0000181096.14257.c2.
181. Sharma AP, Moussa M, Casier S, Rehman F, Filler G, Grimmer J. 2009. Intravenous immunoglobulin as rescue therapy for BK virus nephropathy. Pediatr Transplant 13:123–129. https://doi.org/10.1111/j.1399-3046.2008.00958.x.
182. Smith JM, Jordan SC. 2009. Intravenous immunoglobulin as treatment for BK virus: nephropathy. Pediatr Transplant 13:11–13. https://doi.org/10.1111/j.1399-3046.2008.01105.x.
183. Anyaegbu EI, Almond PS, Milligan T, Allen WR, Gharaybeh S, Al-Akash SI. 2012. Intravenous immunoglobulin therapy in the treatment of BK viremia and nephropathy in pediatric renal transplant recipients. Pediatr Transplant 16:E19–E24. https://doi.org/10.1111/j.1399-3046.2010.01384.x.
184. Shah T, Vu D, Naraghi R, Campbell A, Min D. 2014. Efficacy of intravenous immunoglobulin in the treatment of persistent BK viremia and BK virus nephropathy in renal transplant recipients. Clin Transpl 2014:109–116.
185. Vu D, Shah T, Ansari J, Naraghi R, Min D. 2015. Efficacy of intravenous immunoglobulin in the treatment of persistent BK viremia and BK virus nephropathy in renal transplant recipients. Transplant Proc 47:394–398. https://doi.org/10.1016/j.transproceed.2015.01.012.
186. Gelfand EW. 2012. Intravenous immune globulin in autoimmune and inflammatory diseases. N Engl J Med 367:2015–2025. https://doi.org/10.1056/NEJMra1009433.
187. Sharma BN, Li R, Bernhoff E, Gutteberg TJ, Rinaldo CH. 2011. Fluoroquinolones inhibit human polyomavirus BK (BKV) replication in primary human kidney cells. Antiviral Res 92:115–123. https://doi.org/10.1016/j.antiviral.2011.07.012.
188. Ali SH, Chandraker A, DeCaprio JA. 2007. Inhibition of simian virus 40 large T antigen helicase activity by fluoroquinolones. Antivir Ther 12:1–6.
189. Portolani M, Pietrosemoli P, Cermelli C, Mannini-Palenzona A, Grossi MP, Paolini L, Barbanti-Brodano G. 1988. Suppression of BK virus replication and cytopathic effect by inhibitors of prokaryotic DNA gyrase. Antiviral Res 9:205–218. https://doi.org/10.1016/0166-3542(88)90004-6.
190. Wojciechowski D, Chanda R, Chandran S, Lee B, Webber A, Macaraig M, Tomlanovich S, Vincenti F. 2012. Ciprofloxacin prophylaxis in kidney transplant recipients reduces BK virus infection at 3 months but not at 1 year. Transplantation 94:1117–1123. https://doi.org/10.1097/TP.0b013e31826ec74e.
191. Gabardi S, Waikar SS, Martin S, Roberts K, Chen J, Borgi L, Sheashaa H, Dyer C, Malek SK, Tullius SG, Vadivel N, Grafals M, Abdi R, Najafian N, Milford E, Chandraker A. 2010. Evaluation of fluoroquinolones for the prevention of BK viremia after renal transplantation. Clin J Am Soc Nephrol 5:1298–1304. https://doi.org/10.2215/CJN.08261109.
192. Zaman RA, Ettenger RB, Cheam H, Malekzadeh MH, Tsai EW. 2014. A novel treatment regimen for BK viremia. Transplantation 97:1166–1171. https://doi.org/10.1097/01.TP.0000441825.72639.4f.
193. Lee BT, Gabardi S, Grafals M, Hofmann RM, Akalin E, Aljanabi A, Mandelbrot DA, Adey DB, Heher E, Fan PY, Conte S, Dyer-Ward C, Chandraker A. 2014. Efficacy of levofloxacin in the treatment of BK viremia: a multicenter, double-blinded, randomized, placebo-controlled trial. Clin J Am Soc Nephrol 9:583–589. https://doi.org/10.2215/CJN.04230413.
194. Knoll GA, Humar A, Fergusson D, Johnston O, House AA, Kim SJ, Ramsay T, Chasse M, Pang X, Zaltzman J, Cockfield S, Cantarovich M, Karpinski M, Lebel L, Gill JS. 2014. Levofloxacin for BK virus prophylaxis following kidney transplantation: a randomized clinical trial. JAMA 312:2106–2114. https://doi.org/10.1001/jama.2014.14721.
195. Schold JD, Rehman S, Kayler LK, Magliocca J, Srinivas TR, Meier-Kriesche H-U. 2009. Treatment for BK virus: incidence, risk factors and outcomes for kidney transplant recipients in the United States. Transplant Int 22:626–634. https://doi.org/10.1111/j.1432-2277.2009.00842.x.
196. Wright AJ, Gill JS. 2016. Strategies to prevent BK virus infection in kidney transplant recipients. Curr Opin Infect Dis 29:353–358. https://doi.org/10.1097/QCO.0000000000000278.
197. Riddell SR, Watanabe KS, Goodrich JM, Li CR, Agha ME, Greenberg PD. 1992. Restoration of viral immunity in immunodeficient humans by the adoptive transfer of T cell clones. Science 257:238–241. https://doi.org/10.1126/science.1352912.
198. Icheva V, Kayser S, Wolff D, Tuve S, Kyzirakos C, Bethge W, Greil J, Albert MH, Schwinger W, Nathrath M, Schumm M, Stevanovic S, Handgretinger R, Lang P, Feuchtinger T. 2013. Adoptive transfer of Epstein-Barr virus (EBV) nuclear antigen 1-specific T cells as treatment for EBV reactivation and lymphoproliferative disorders after allogeneic stem-cell transplantation. J Clin Oncol 31:39–48. https://doi.org/10.1200/JCO.2011.39.8495.
199. Cobbold M, Khan N, Pourgheysari B, Tauro S, McDonald D, Osman H, Assenmacher M, Billingham L, Steward C, Crawley C, Olavarria E, Goldman J, Chakraverty R, Mahendra P, Craddock C, Moss PA. 2005. Adoptive transfer of cytomegalovirus-specific CTL to stem cell transplant patients after selection by HLA-peptide tetramers. J Exp Med 202:379–386. https://doi.org/10.1084/jem.20040613.
200. Balduzzi A, Lucchini G, Hirsch HH, Basso S, Cioni M, Rovelli A, Zincone A, Grimaldi M, Corti P, Bonanomi S, Biondi A, Locatelli F, Biagi E, Comoli P. 2011. Polyomavirus JC-targeted T-cell therapy for progressive multiple leukoencephalopathy in a hematopoietic cell transplantation recipient. Bone Marrow Transplant 46:987–992. https://doi.org/10.1038/bmt.2010.221.
201. Khanna R, Bell S, Sherritt M, Galbraith A, Burrows SR, Rafter L, Clarke B, Slaughter R, Falk MC, Douglass J, Williams T, Elliott SL, Moss DJ. 1999. Activation and adoptive transfer of Epstein-Barr virus-specific cytotoxic T cells in solid organ transplant patients with posttransplant lymphoproliferative disease. Proc Natl Acad Sci U S A 96:10391–10396. https://doi.org/10.1073/pnas.96.18.10391.
202. Crough T, Beagley L, Smith C, Jones L, Walker DG, Khanna R. 2012. Ex vivo functional analysis, expansion and adoptive transfer of cytomegalovirus-specific T-cells in patients with glioblastoma multiforme. Immunol Cell Biol 90:872–880. https://doi.org/10.1038/icb.2012.19.
203. Khanna R, Smith C. 2013. Cellular immune therapy for viral infections in transplant patients. Indian J Med Res 138:796–807.
204. Moosmann A, Bigalke I, Tischer J, Schirrmann L, Kasten J, Tippmer S, Leeping M, Prevalsek D, Jaeger G, Ledderose G, Mautner J, Hammerschmidt W, Schendel DJ, Kolb HJ. 2010. Effective and long-term control of EBV PTLD after transfer of peptide-selected T cells. Blood 115:2960–2970. https://doi.org/10.1182/blood-2009-08-236356.
205. Schmitt A, Tonn T, Busch DH, Grigoleit GU, Einsele H, Odendahl M, Germeroth L, Ringhoffer M, Ringhoffer S, Wiesneth M, Greiner J, Michel D, Mertens T, Rojewski M, Marx M, von Harsdorf S, Dohner H, Seifried E, Bunjes D, Schmitt M. 2011. Adoptive transfer and selective reconstitution of streptamer-selected cytomegalovirus-specific CD8+ T cells leads to virus clearance in patients after allogeneic peripheral blood stem cell transplantation. Transfusion 51:591–599. https://doi.org/10.1111/j.1537-2995.2010.02940.x.
206. Feuchtinger T, Opherk K, Bethge WA, Topp MS, Schuster FR, Weissinger EM, Mohty M, Or R, Maschan M, Schumm M, Hamprecht K, Handgret-

inger R, Lang P, Einsele H. 2010. Adoptive transfer of pp65-specific T cells for the treatment of chemorefractory cytomegalovirus disease or reactivation after haploidentical and matched unrelated stem cell transplantation. Blood 116:4360–4367. https://doi.org/10.1182/blood-2010-01-262089.
207. Papadopoulou A, Gerdemann U, Katari UL, Tzannou I, Liu H, Martinez C, Leung K, Carrum G, Gee AP, Vera JF, Krance RA, Brenner MK, Rooney CM, Heslop HE, Leen AM. 2014. Activity of broad-spectrum T cells as treatment for AdV, EBV, CMV, BKV, and HHV6 infections after HSCT. Sci Transl Med 6:242ra283. https://doi.org/10.1126/scitranslmed.3008825.
208. Dasari V, Schuessler A, Smith C, Wong Y, Miles JJ, Smyth MJ, Ambalathingal G, Francis R, Campbell S, Chambers D, Khanna R. 2016. Prophylactic and therapeutic adenoviral vector-based multivirus-specific T-cell immunotherapy for transplant patients. Mol Ther Methods Clin Dev 3:16058. https://doi.org/10.1038/mtm.2016.58.
209. O'Reilly RJ, Lee FK, Grossbard E, Kapoor N, Kirkpatrick D, Dinsmore R, Stutzer C, Shah KV, Nahmias AJ. 1981. Papovavirus excretion following marrow transplantation: incidence and association with hepatic dysfunction. Transplant Proc 13:262–266.
210. Arthur RR, Shah KV, Baust SJ, Santos GW, Saral R. 1986. Association of BK viruria with hemorrhagic cystitis in recipients of bone marrow transplants. N Engl J Med 315:230–234. https://doi.org/10.1056/NEJM198607243150405.
211. Dropulic LK, Jones RJ. 2008. Polyomavirus BK infection in blood and marrow transplant recipients. Bone Marrow Transplant 41:11–18. https://doi.org/10.1038/sj.bmt.1705886.
212. Erard V, Kim HW, Corey L, Limaye A, Huang ML, Myerson D, Davis C, Boeckh M. 2005. BK DNA viral load in plasma: evidence for an association with hemorrhagic cystitis in allogeneic hematopoietic cell transplant recipients. Blood 106:1130–1132. https://doi.org/10.1182/blood-2004-12-4988.
213. Pavlakis M, Haririan A, Klassen DK. 2006. BK virus infection after non-renal transplantation. Adv Exp Med Biol 577:185–189. https://doi.org/10.1007/0-387-32957-9_13.
214. Bogdanovic G, Priftakis P, Giraud G, Kuzniar M, Ferraldeschi R, Kokhaei P, Mellstedt H, Remberger M, Ljungman P, Winiarski J, Dalianis T. 2004. Association between a high BK virus load in urine samples of patients with graft-versus-host disease and development of hemorrhagic cystitis after hematopoietic stem cell transplantation. J Clin Microbiol 42:5394–5396. https://doi.org/10.1128/JCM.42.11.5394-5396.2004.
215. Wong AS, Chan KH, Cheng VC, Yuen KY, Kwong YL, Leung AY. 2007. Relationship of pretransplantation polyoma BK virus serologic findings and BK viral reactivation after hematopoietic stem cell transplantation. Clin Infect Dis 44:830–837. https://doi.org/10.1086/511863.
216. Randhawa PS. 2005. Anti-BK virus activity of ciprofloxacin and related antibiotics. Clin Infect Dis 41:1366–1367. https://doi.org/10.1086/497080.
217. Leung AY, Chan MT, Yuen KY, Cheng VC, Chan KH, Wong CL, Liang R, Lie AK, Kwong YL. 2005. Ciprofloxacin decreased polyoma BK virus load in patients who underwent allogeneic hematopoietic stem cell transplantation. Clin Infect Dis 40:528–537. https://doi.org/10.1086/427291.
218. Weinreb DB, Desman GT, Amolat-Apiado MJ, Burstein DE, Godbold JH, Jr, Johnson EM. 2006. Polyoma virus infection is a prominent risk factor for bladder carcinoma in immunocompetent individuals. Diagn Cytopathol 34:201–203. https://doi.org/10.1002/dc.20429.
219. Newton R, Ribeiro T, Alvarez E, Ziegler J, Casabonne D, Carpenter L, Beral V, Mbidde E, Parkin DM, Wabinga H, Mbulaiteye S, Jaffe H, Touze A, Coursaget P, Uganda Kaposi's and Sarcoma Study Group. 2006. BK virus and cancer in Uganda. Eur J Cancer Prev 15:285–289. https://doi.org/10.1097/00008469-200608000-00002.
220. Toptan T, Yousem SA, Ho J, Matsushima Y, Stabile LP, Fernández-Figueras M-T, Bhargava R, Ryo A, Moore PS, Chang Y. 2016. Survey for human polyomaviruses in cancer. JCI Insight 1:e85562.
221. Bocchetta M, Eliasz S, De Marco MA, Rudzinski J, Zhang L, Carbone M. 2008. The SV40 large T antigen-p53 complexes bind and activate the insulin-like growth factor-I promoter stimulating cell growth. Cancer Res 68:1022–1029. https://doi.org/10.1158/0008-5472.CAN-07-5203.
222. Topalis D, Andrei G, Snoeck R. 2013. The large tumor antigen: a "Swiss Army knife" protein possessing the functions required for the polyomavirus life cycle. Antiviral Res 97:122–136. https://doi.org/10.1016/j.antiviral.2012.11.007.
223. Fioriti D, Pietropaolo V, Dal Forno S, Laurenti C, Chiarini F, Degener AM. 2003. Urothelial bladder carcinoma and viral infections: different association with human polyomaviruses and papillomaviruses. Int J Immunopathol Pharmacol 16:283–288. https://doi.org/10.1177/039463200301600315.
224. Das D, Wojno K, Imperiale MJ. 2008. BK virus as a cofactor in the etiology of prostate cancer in its early stages. J Virol 82:2705–2714. https://doi.org/10.1128/JVI.02461-07.
225. Das D, Shah RB, Imperiale MJ. 2004. Detection and expression of human BK virus sequences in neoplastic prostate tissues. Oncogene 23:7031–7046. https://doi.org/10.1038/sj.onc.1207920.
226. Sontag E, Fedorov S, Kamibayashi C, Robbins D, Cobb M, Mumby M. 1993. The interaction of SV40 small tumor antigen with protein phosphatase 2A stimulates the MAP kinase pathway and induces cell proliferation. Cell 75:887–897. https://doi.org/10.1016/0092-8674(93)90533-V.
227. Trabanelli C, Corallini A, Gruppioni R, Sensi A, Bonfatti A, Campioni D, Merlin M, Calza N, Possati L, Barbanti-Brodano G. 1998. Chromosomal aberrations induced by BK virus T antigen in human fibroblasts. Virology 243:492–496. https://doi.org/10.1006/viro.1998.9080.
228. Corallini A, Altavilla G, Cecchetti MG, Fabris G, Grossi MP, Balboni PG, Lanza G, Barbanti-Brodano G. 1978. Ependymomas, malignant tumors of pancreatic islets, and osteosarcomas induced in hamsters by BK virus, a human papovavirus. J Natl Cancer Inst 61:875–883.
229. Kenan DJ, Mieczkowski PA, Burger-Calderon R, Singh HK, Nickeleit V. 2015. The oncogenic potential of BK-polyomavirus is linked to viral integration into the human genome. J Pathol 237:379–389. https://doi.org/10.1002/path.4584.
230. Lau SK, Lacey SF, Chen YY, Chen WG, Weiss LM. 2007. Low frequency of BK virus in prostatic adenocarcinomas. APMIS 115:743–749. https://doi.org/10.1111/j.1600-0463.2007.apm_601.x.
231. Sfanos KS, Sauvageot J, Fedor HL, Dick JD, De Marzo AM, Isaacs WB. 2008. A molecular analysis of prokaryotic and viral DNA sequences in prostate tissue from patients with prostate cancer indicates the presence of multiple and diverse microorganisms. Prostate 68:306–320. https://doi.org/10.1002/pros.20680.
232. Sundsfjord A, Spein AR, Lucht E, Flaegstad T, Seternes OM, Traavik T. 1994. Detection of BK virus DNA in nasopharyngeal aspirates from children with respiratory infections but not in saliva from immunodeficient and immunocompetent adult patients. J Clin Microbiol 32:1390–1394.
233. Bofill-Mas S, Pina S, Girones R. 2000. Documenting the epidemiologic patterns of polyomaviruses in human populations by studying their presence in urban sewage. Appl Environ Microbiol 66:238–245. https://doi.org/10.1128/AEM.66.1.238-245.2000.
234. Taguchi F, Nagaki D, Saito M, Haruyama C, Iwasaki K. 1975. Transplacental transmission of BK virus in human. Jpn J Microbiol 19:395–398. https://doi.org/10.1111/j.1348-0421.1975.tb00897.x.
235. Taguchi F, Kajioka J, Shimada N. 1985. Presence of interferon and antibodies to BK virus in amniotic fluid of normal pregnant women. Acta Virol 29:299–304.
236. Boldorini R, Allegrini S, Miglio U, Nestasio I, Paganotti A, Veggiani C, Monga G, Pietropaolo V. 2010. BK virus sequences in specimens from aborted fetuses. J Med Virol 82:2127–2132. https://doi.org/10.1002/jmv.21923.
237. Dadhania D, Snopkowski C, Ding R, Muthukumar T, Chang C, Aull M, Lee J, Sharma VK, Kapur S, Suthanthiran M. 2008. Epidemiology of BK virus in renal allograft recipients: independent risk factors for BK virus replication. Transplantation 86:521–528. https://doi.org/10.1097/TP.0b013e31817c6447.
238. Sood P, Senanayake S, Sujeet K, Medipalli R, Zhu YR, Johnson CP, Hariharan S. 2012. Management and outcome of BK viremia in renal transplant recipients: a prospective single-center study. Transplantation 94:814–821. https://doi.org/10.1097/TP.0b013e31826690c6.
239. Barbosa D, Kahwaji J, Puliyanda D, Mirocha J, Reinsmoen N, Lai CH, Villicana R, Peng A, Jordan SC, Vo A, Toyoda M. 2014. Polyomavirus BK viremia in kidney transplant recipients after desensitization with IVIG and rituximab. Transplantation 97:755–761. https://doi.org/10.1097/01.TP.0000437671.78716.f3.
240. Schwarz A, Linnenweber-Held S, Heim A, Framke T, Haller H, Schmitt C. 2016. Viral origin, clinical course, and renal outcomes in patients with BK virus infection after living-donor renal transplantation. Transplantation 100:844–853. https://doi.org/10.1097/TP.0000000000001066.
241. Sawinski D, Forde KA, Trofe-Clark J, Patel P, Olivera B, Goral S, Bloom RD. 2015. Persistent BK viremia does not increase intermediate-term graft loss but is associated with de novo donor-specific antibodies. J Am Soc Nephrol 26:966–975. https://doi.org/10.1681/ASN.2014010119.

242. Thamboo TP, Jeffery KJM, Friend PJ, Turner GDH, Roberts ISD. 2007. Urine cytology screening for polyoma virus infection following renal transplantation: the Oxford experience. J Clin Pathol 60:927–930.
243. Ma MK, Leung AY, Lo KY, Lio WI, Chan HW, Wong I, Hau AK, Tam CH, Wong AK, Kuok UI, Chau KF, Fung SK, Kwan TH, Wong SS, Tang SC. 2015. Screening algorithm for BK virus-associated nephropathy using sequential testing of urinary cytology: a probabilistic model analysis. Am J Nephrol 42:410–417. https://doi.org/10.1159/000443514.
244. Ranzi AD, Prolla JC, Keitel E, Brackmann R, Kist R, dos Santos G, Bica CG. 2012. The role of urine cytology for 'decoy cells' as a screening tool in renal transplant recipients. Acta Cytol 56:543–547. https://doi.org/10.1159/000341425.
245. Costa C, Bergallo M, Astegiano S, Terlizzi ME, Sidoti F, Segoloni GP, Cavallo R. 2008. Monitoring of BK virus replication in the first year following renal transplantation. Nephrol Dial Transplant 23:3333–3336. https://doi.org/10.1093/ndt/gfn289.
246. Marinic K, Sinchi J, Gómez M, Díaz R, Grillo S, Habegger-de Sorrentino A. 2014. Monitoring of BK virus in transplant patients of the renal unit of the Perrando Hospital, Chaco, Argentina. Nefrologia 34:799–800. https://doi.org/10.3265/Nefrologia.pre2014.Jul.12657.
247. Huang G, Wang C-X, Zhang L, Fei J-G, Deng S-X, Qiu J, Li J, Chen G-D, Fu Q, Chen L-Z. 2015. Monitoring of polyomavirus BK replication and impact of preemptive immunosuppression reduction in renal-transplant recipients in China: a 5-year single-center analysis. Diagn Microbiol Infect Dis 81:21–26. https://doi.org/10.1016/j.diagmicrobio.2014.09.024.
248. Kuten SA, Patel SJ, Knight RJ, Gaber LW, DeVos JM, Gaber AO. 2014. Observations on the use of cidofovir for BK virus infection in renal transplantation. Transplant Infect Dis 16:975–983. https://doi.org/10.1111/tid.12313.
249. Tylden GD, Hirsch HH, Rinaldo CH. 2015. Brincidofovir (CMX001) inhibits BK polyomavirus replication in primary human urothelial cells. Antimicrob Agents Chemother 59:3306–3316. https://doi.org/10.1128/AAC.00238-15.
250. Nesselhauf N, Strutt J, Bastani B. 2016. Evaluation of leflunomide for the treatment of BK viremia and biopsy proven BK nephropathy; a single center experience. J Nephropathol 5:34–37. https://doi.org/10.15171/jnp.2016.06.
251. Lebreton M, Esposito L, Mengelle C, Del Bello A, Delarche A, Dorr G, Milongo D, Marion O, Izopet J, Kamar N. 2016. A 3-month course of ciprofloxacin does not prevent BK virus replication in heavily immunosuppressed kidney-transplant patients. J Clin Virol 79:61–67. https://doi.org/10.1016/j.jcv.2016.04.004.
252. Tzannou I, Papadopoulou A, Watanabe A, Kuvalekar M, Gee AP, Naik S, Martinez C, Leung KS, Sasa GS, Krance RA, Carrum G, Ramos CA, Grilley B, Brenner MK, Rooney CM, Heslop HE, Leen AM, Omer B. 2016. Administration of most closely HLA-matched multivirus-specific T cells for the treatment of EBV, CMV, AdV, HHV6, and BKV post allogeneic hematopoietic stem cell transplant, abstr S45. Abstr 58th Am Soc Hematol Annu Meet, San Diego, CA.

George R. Ambalathingal is a Ph.D. graduate student at the QIMR Berghofer Medical Research Institute/University of Queensland, Brisbane, Australia. He completed his bachelor's degree in technology at Anna University, India, followed by a master's degree in engineering in biotechnology from Satyabhama University, India. Before starting his Ph.D. program, he worked as a Scientist in the Discovery Biology Division of Anthem Biosciences Ltd. His current research focuses on characterizing the functions of BKV-specific T cells in comparison to other virus-specific T cells.

Ross S. Francis is a Consultant Nephrologist and Transplant Physician at Princess Alexandra Hospital in Brisbane, Australia. His clinical and research interests range from translation of novel treatments for immunological kidney disease and transplantation, including biological and cellular therapies, to improving transition care for young adults with kidney disease. He is a council member for the Australian and New Zealand Society of Nephrology (ANZSN) and a member of the Australasian Kidney Trials Network Transplantation Working Group and represents ANZSN on the Renal Transplant Advisory Committee of the Transplantation Society of Australia and New Zealand.

Mark J. Smyth is a Senior Scientist and Immunology Coordinator at the QIMR Berghofer Medical Research Institute. He completed his Ph.D. studies in 1988 and trained at the National Cancer Institute (NCI) (1988 to 1992) before commencing his independent research career in Australia. Over the last 15 years, he has rekindled worldwide interest in cancer immune surveillance and defined immune-mediated dormancy of cancer. Historically, his work on natural killer (NK) cells and immunoregulation has been extended to host antiviral responses, and more recently, he provided a new means of classifying NK cell subtypes.

Corey Smith completed his Ph.D. studies in 2004 at the University of Melbourne and then took up a research position at the QIMR Berghofer Medical Research Institute. His work focuses on the development of immunotherapeutic approaches to treat disease and cancer associated with persistent viral infection. This has led to the commencement of a number of adoptive immunotherapy studies. His work has also focused on understanding the mechanisms that influence the efficient induction of T cell responses to persistent human viral infections and the role that immune evasion strategies play in virus-associated cancer and disease.

Continued next page

Rajiv Khanna is a Senior Scientist and Senior Principal Research Fellow at the QIMR Berghofer Medical Research Institute. He has extensive expertise in immunotherapy clinical trials, cancer immunology, and vaccine development. Over the last 2 decades, his group has successfully translated his research towards the development of novel T cell-based immunotherapeutic strategies for the treatment of cancer patients and transplant recipients. Professor Khanna has been invited by the International Transplant Society to participate in the development of guidelines for the clinical management of cytomegalovirus infection in solid organ transplant patients.