Pathogenicity of BK virus on the urinary system

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Introduction
The polyomaviruses are omnipresent in nature. The major sites of BK virus appearance are the kidney tubular epithelial cells and urinary bladder surface transitional cells.

Material and methods
A literature search according to PRISMA guidelines within the Medline database was conducted in July 2019 for articles presenting data about BK virus in urologic aspect without setting time limits, using the terms ‘BK virus’ in conjunction with transplantation, nephropathy, stenosis, cancer, bladder, prostate, kidney.

Results
The BK virus usually stays latent, however, its replication may become active in various clinical situations of impaired immunocompetence such as solid organ transplantation, bone marrow transplantation, AIDS, pregnancy, multiple sclerosis, administration of chemotherapy or biologic therapy. BK virus is associated with two main complications after transplantation: polyomavirus-associated nephropathy in kidney transplant patients and polyomavirus-associated hemorrhagic cystitis in allogeneic hematopoietic stem cell transplant patients.

Conclusions
The aim of this article was to present available data on urologic aspects of BK virus infection, its detection methods and available treatment.

Key Words: polyomavirus · BK virus · urology · haemorrhagic cystitis · polyomavirus associated nephropathy

INTRODUCTION

According to the International Committee on Taxonomy of Viruses, polyomaviridae is a family with 89 recognized virus species contained within four genera, as well as 9 species that could not be assigned to any genus [1]. Among all polyomaviridae 13 species are known to infect humans [2, 3]. Most of these viruses are very common in the human population, yet, involvement of these viruses in human pathologies is rare. The polyomaviruses are omnipresent in nature and species specific – they infect humans (JCV, BKV), monkeys (simian virus 40 SV40), and mice (mouse polyomavirus) [4]. BK virus (BKV) is a ubiquitous polyoma virus, often acquired during childhood with a 80–90% seroprevalence rate among adults. The major sites of BKV appearance are the kidney tubular epithelial cells and urinary bladder surface transitional cells. It usually stays latent, however, BKV replication may become active in various clinical situations of impaired immunocompetence such as solid organ transplantation, bone marrow transplantation, AIDS, pregnancy, multiple sclerosis, administration of chemotherapy or biologic therapy [5]. Nowadays, with the use of potent immunosuppressive agents and enhanced viral surveillance protocols, the BKV has arisen as an important cause of morbidity in renal transplant recipients. BKV is associated with two main complications after transplantation: polyomavirus-associated nephropathy (BKVAN) in 1 to 10% of kidney transplant pa-
tients [6–9] and polyomavirus-associated haemorrhagic cystitis (BKVHC) in 5 to 15% of allogeneic hematopoietic stem cell transplant (HSCT) patients [10, 11, 12]. Also, other complications such as ureteral stenosis and some cancers are related to BKV infection [4, 13–16]. Despite being rare, BKV associated pathologies also occur in patients with non-kidney solid organ transplantation (SOT) or with inherited, acquired or drug-induced immunodeficiency [13, 17]. Besides BKVAN and BKVHC they include pneumonitis, retinitis, liver disease and meningoencephalitis [18].

The aim of this article is to present available data on urologic aspects of BK virus infection, its detection and treatment.

**Evidence acquisition and evidence synthesis**

A literature search according to PRISMA guidelines within the Medline database was conducted in July 2019 for articles presenting data about BK virus in urologic aspect without setting time limits, using the terms ‘BK virus’ in conjunction with transplantation, nephropathy, stenosis, cancer, bladder, prostate, kidney. Boolean operators (NOT, AND, OR) were also used in succession to narrow and broaden the search. Autoalerts in Medline were also run, as well as reference lists of original articles and review articles for further eligible data. The search was limited to English literature. Articles that did not address the topics were excluded, and the full text of the remaining articles was subsequently reviewed.

**The BK virus**

The term ‘BK’ originated from a patient’s initials, in whom the virus was first detected in 1971. The ‘first’ patient underwent renal transplantation 3 months earlier and presented with anuria and pain over the graft [19]. Diagnostic workup revealed ureteric obstruction that was later corrected surgically. Examination of biological samples and of the ureteral segment excised during surgery exposed a previously unknown virus. With time, other research confirmed an association between renal transplant recipients’ morbidity and BKV incidence [20–23].

**Genome**

Polyomaviruses are small (45 nm) non-enveloped viruses that are composed of 72 capsomers with icosahedral symmetry, harbour a circular double-stranded DNA, and belong to the Polyomaviridae family with Polyomavirus as the only genus. The BK virus’s genetic material contains three main domains: (1) an early region composed of replicative genes – large tumour antigen (T antigen) and small tumour antigens (t antigen); (2) a non-coding control region (NCCR) adjacent to the early region containing transcription factors for the early and late genes and (3) a late region encoding the viral capsid proteins (VP1,VP2, VP3) [18, 24]. The BKV genome is in 75% homologous with the JC virus genome and in 70% with SV40 virus genome [24]. BKV has four serologic types based on sequence variation in the genomic region of VP1, which can be further divided into various subtypes. Type I presents the highest prevalence of 70–80% and is followed by type IV (10–20%), with some geographical distinctions [25, 26]. Apart from the VP1 region subdivision, there are also other subclassifications of BKV due to the variation in the NCCR [5]. However, despite many subtypes of BKV being described, the clinical implications of infection with the different genotypes of BKV are still unknown [27].

**Epidemiology**

It is estimated that BK virus seroprevalence concerns 50% of children under 5 years old and up to 90% of the adult population [16, 28]. The primary BKV infection often occurs around the age of 3 to 4 years old [29]. The virus can be transmitted via various routes including: faecal-oral, respiratory, through blood transfusions, organ transplantation, transplacentally and through seminal fluid [30]. After infection (with or without trivial symptoms), BKV is not completely eliminated from the host and may be detected in renal tubular epithelial cells, where it remains latent lifelong with replication controlled by the immune system [31]. Other locations of the virus include the liver, lungs, brain and lymph nodes. Asymptomatic and clinically insignificant viruria occurs in healthy patients with occurrence up to 20%, with higher incidences during immunosuppressed states and in pregnancy [16, 30].

In renal transplantation, reactivation of latent virus starts soon after immunosuppression implementation, and is observed in up to 30–50% of kidney recipients within the first three months. The precise mechanism of infection reactivation is not well elucidated [32]. The risk of reactivation depends on the microbiologic features of the virus, the presence of inducing factors for the activation of virus in tissues (kidney injury, graft rejection, ischemia, drug toxicity), the amount of virus present, the nature of the person’s immune deficits (e.g. serological status), total burden of immunosuppression and host–graft relationship variations [18, 33].
Clinical presentations

BK Virus Nephropathy

BKVAN concerns mostly patients after kidney transplantation. Despite the fact that 30–50% of all renal recipients develop temporary BK viruria and approximately one-third present viremia, only 1–10% of patients progress to BKVAN [34, 35]. Rarely, BKVAN may also appear in native kidneys of other organs recipients – lung, heart, liver and pancreas, as well as bone marrow transplant recipients, haemorrhagic cystitis is the most common feature of BKV infection.

In renal transplant recipients the deterioration of allograft function is often the first and the sole sign of BKVAN. In more than 50% of kidney transplant recipients, BKVAN leads to graft failure and in 30 to 80% of cases – graft loss [37, 45]. The majority of BKVAN cases occur within the first 12 months after transplantation, however, 25% of cases may be diagnosed long after transplantation.

Multiple complementary risk factors contribute to disease progression. From amongst viral-related factors, serotype and genomic mutations (NCCR rearrangements) were proven to be relevant. Also, recipient characteristics (older age, male gender, ethnicity, HLA-C7 negativity, BK-virus seronegativity before transplantation, low number of BKV-specific T-cells and co-morbidity with diabetes mellitus), previous acute rejection episodes, delayed graft function, ureteral injury during transplantation procedure were describe to increase the risk of BKVAN with donor-related factors including BKV seropositivity and donor-recipient HLA mismatching [16, 46, 47]. In addition to the above, the total degree of immunosuppression is thought to be the most important factor promoting BKV reactivation and no single immunosuppressive agent was proven to increase the rate of BKVAN. However, patients receiving tacrolimus-based immunosuppression have been reported to have higher rates of BKVAN than those on cyclosporine or sirolimus [5, 48, 49].

Diagnosis of BKVAN

Historically, the diagnosis of polyomavirus infection was based on the demonstration of rising antibody titers (which was later proved not to be clinically relevant), cytologic evaluation of urine sediment, viral isolation from urine and blood and electron/immuno-electron microscopic studies of urine and immuno-histochemical staining for SV40 LTag (Simian Vacuolating Virus 40 T Antigen) in kidney biopsy. Cytologic evaluation of urine sediment can demonstrate viral inclusion bearing epithelial cells, so-called ‘decoy cells’ (characterized by a ground-glass appearance with an enlarged nucleus, which is occupied by a homogeneous basophilic inclusion surrounded by chromatin). They are present in 40% to 60% of renal transplant recipients, although positive predictive value is approximately 20% with negative predictive value of 100% [50]. Virus particles are also detectable by direct negative staining electron microscopy (BKV-clusters – ‘haufen’) [22, 51]. BKV infection after kidney transplantation may progress gradually from initial viruria through viremia and in a subgroup of 20–40% of viremic patients to histological changes classified as BKVAN [52]. Currently, BKVAN diagnosis is based on PCR-based viral load analysis in the plasma and urine. Both quantitative and qualitative tests are being used, with later being much more sensitive. Sustained high urine viral loads of \(>7_{10} \text{ copies/ml} \) correlate with the onset of viremia [53]. Sustained plasma BKV-DNA load higher than \(4_{10} \text{ copies/ml} \) is considered as presumptive BKVAN [54, 55, 56]. Literature data indicate that the urine BKV DNA \(>7_{log} \text{ copies/ml} \) and/or plasma BKV DNA \(>4_{log} \text{ copies/ml} \) indicate possibility of BKVAN even in the absence of demonstrable BKV replication in renal biopsies [12, 57, 58]. It was also reported that measurement of messenger RNA for BK virus VP1 in urine can mirror active viral replication [59, 60].

Although helpful in identifying patients at increased risk, laboratory assays including quantitative PCR testing are not perfect in rendering a definitive diagnosis of BKVAN.

Biopsies in patients with presumptive BKVAN are obtained routinely to confirm a diagnosis of definitive BKVAN and evaluate the degree of tissue injury. The term ‘definitive’ BKVAN describes only patients with biopsy-proven BKV-related nephropathy [61]. BKVAN is characterized by subacute virus-induced tubular injury, inflammation, and progressive nephron damage. Histologic markers of BKVAN include viral cytopathic effect with large, homogenous intranuclear inclusions, mainly in tubular epithelium with no necrosis. BKVAN include ischemic glomerulopathy, dilation of glomerular capillaries or mild increase in mesangial matrix, also cytopathic effect in parietal Bowman capsule, crescents or glomerulonephritis is present [62, 63]. Diagnostic confirmation obtained by immunohistochemistry (IHC) with a positive SV40 LTag staining reaction is required. Presence of SV40 LTag in epithelial cell nuclei is
often but not always accompanied by the typical intranuclear viral inclusion bodies [52].

**Screening for prevention**

It is widely known that early intervention in the situation of BKV infection/reactivation in immunocompromised patients is effective in preventing the development of severe complications. Because of this, BKVAN surveillance is therefore recommended for renal transplant recipients. Screening for BKV infection may be performed by means of urine cytology (decoy cells) or preferably by PCR assessment of urine and/or plasma. It has to be remembered that methods of screening are burdened with the same problems as diagnostic methods such as interassay variation, interobserver variability and lack of universal standardization. For that reason the optimal frequency and method for BKV surveillance are not clear. The screening schedules vary between different centres. According to the 2019 American Society of Transplantation Infectious Diseases Guidelines screening for BKV replication should be performed in all kidney recipients monthly until month 9, and then at least every 3 months during the first two years post-transplant, and then with decreasing frequency until the fifth year post-transplant, yet, the screening procedures may be employed more frequently in special circumstances (any unexplained graft dysfunction, in regions with higher BKVAN incidence) [53, 57, 64–67]. In recipients with viral urine load >7 log10 copies/ml and/or urine cytology >3 decoy cells HPF evaluation of viremia is required. In case of viremia >4 log10 copies/ml confirmation by kidney biopsy and reduction of immunosuppression should be considered [52].

**Treatment**

BK virus pathogenicity is for a great part due to the importance of its replication, supported by immunosuppression (iatrogenic, secondary to HIV infection, etc.). Therefore, an early diagnosis and a rapid restoration of immunity leading to limitation of viral replication, is currently the most effective way to control the disease [68]. Stepwise immunosuppression reduction is recommended for kidney transplant recipients with viruria >3 log10 copies/ml for 3 weeks or increasing to >4 log10 copies/ml and in all cases of for biopsy proven BKVAN [53]. Although there is no standard way to reduce immunosuppression, most centres start from discontinuation of mycophenolate mofetil/sodium or azathioprine and reduction of calcineurin inhibitor dose by 25% to 50%. Switching from tacrolimus to cyclosporine A (trough levels 100-150 ng/ml) may be also effective as well as switching to mTOR inhibitors [69]. It is recommended to monitor the response by viruria and viremia assessment every 2–4 weeks. After this, clearance of viruria and viremia in achieved in most of the patients, yet, the kidney allograft function do not always return to normal levels [70, 71].

Additional administration of antiviral therapy such as cidofovir at low doses, leflunomide, quinolones, artesunate and intravenous immunoglobulins was reported, but the, above mentioned agents were not clearly proved to be more efficacious than screening and reduction of immunosuppressive therapy [72–81].

**Ureteral stenosis**

Ureteral stenosis with fibrosis, and ulceration of the donor ureter after renal transplantation associated with BKV infection, although rare (2 to 6%), is a challenging complication which often requires surgical correction [21, 82, 83]. It is usually clinically asymptomatic with progressing oliguria and impaired renal function. Classic colic symptoms or discomfort over the graft are not present in all cases, since the transplanted kidney is denervated [84]. Risk factors of stenosis development do not vary from general risk factors of BKV infection reactivation. It was reported that use of ureteral stents after transplantation increase rate of polyomavirus nephropathy. It was also shown that stent placement, yet not the time of removal, was lined to BKV viremia. In light of those observations routine placement of ureteral stents during transplantation is a subject of debate [85–88]. Additionally, ischemia of the ureter resulting from stripping, long ureter or imperfect uretero-vesical anastomosis may play role in BKV related stricture.

Treatment include administration of medical regimens similar to those used in BKVAN. In cases of obstructive nephropathy the proper renal drainage by DJ catheter or percutaneous nephrostomy is required. Further endoscopic dilatation, long-term stenting and/or surgical resection of stricutured segment are possible therapeutic options.

**BK Virus haemorrhagic cystitis**

Haemorrhagic cystitis (HC) is a complication of BKV infection mainly related to hematopoietic stem cell transplant, yet, it may also appear in other immunocompromised patients [89, 90]. BKV viruria is pres-
ent in the majority of bone marrow transplant recipients and about 10–30% of patients develop clinically significant HC mainly shortly after the procedure [12, 91, 92, 93]. Various risk factors of HC incidence and severity have been identified including donor–recipient gender mismatches, bone marrow as a stem cell source, class II and III of thalassemia, use of busulfan plus cyclophosphamide plus ATG in the conditioning regimen, graft-versus-host disease (GVHD), use of prednisolone and cyclosporine as prophylaxis treatment of GVHD, and gancyclovir and intravenous immunoglobulin (IVIg) as antiviral drugs [91].

HC may present with haematuria of varying severity, lower urinary tract symptoms (dysuria, urgency, frequency) and suprapubic pain. In more advanced cases, blood clots can deposit in the urinary tract leading to acute urinary retention, obstructive uropathy and finally, renal function impairment. Clinical severity of HC can be graded according to the following criteria: grade 0 (no haematuria), grade I (microscopic haematuria), grade II (macroscopic haematuria), grade III (macroscopic haematuria with presence of blood clots), and grade IV (macroscopic haematuria with clots and renal impairment due to urinary obstruction) [11, 94].

The diagnosis is often done by exclusion basing on clinical presentation and BKV viral load and urine analysis. It is worth mentioning that plasma BKV load in HC may be undetectable [94].

Definitive therapeutic options for HC are not well established. Treatment is mainly symptomatic with hyperhydration, forced diuresis and pain management. Therapy similar to that used in BKVN may be administered, including modification of immunosuppressive medications and the use of cidofovir, lefunomide, and fluoroquinolone antibiotics. Some cases of severe bleeding require catheter placement, bladder irrigation, hyperbaric oxygen and in some life-threatening situations, blood transfusions and endoscopic treatment with electric/laser fulguration, vascular embolization or cystectomy if needed [95]. In patients with obstructive nephropathy, DJ or PCN placement may be necessary.

**Oncogenesis**

Patients after renal transplantation harbour a higher risk of cancer when compared with the general population, and an immunosuppressed state has been linked with an increased risk of virus-related malignancies [96]. However, despite the fact that BKV DNA has been discovered in a various tumour tissues, the relation between BKV infection and malignancy (especially prostate and bladder cancer) is a subject of intense discussion [97]. It is unclear whether this is the result of a predisposition for viral uptake into tumour cells or rather a causative mechanism. Moreover, multiple in-vitro and in-vivo animal studies show clear oncogenic impact of BKV in creatures ranging from mice to raccoons [98]. Yet, the results of those studies cannot be translated directly into humans.

It has been postulated that the oncogenic role of BKV is based on the expression of early coding viral replication proteins - large T antigen and small T antigen, which can begin neoplastic transformation of infected cells. T antigens are identified to be prooncogenic due to their ability to inactivate tumour suppressor proteins, such as p53 and pRb (retinoblastoma protein). By that, BKV pushes the infected cell into an ‘S’ cell cycle phase and inhibits its apoptosis ability. It further leads to increased cell proliferation, immortalization and neoplastic transformation [5, 99–101]. Other BKV pro-oncogenic mechanisms are also proposed and include induction of telomerase activity, deregulation of multiple crucial signalling pathways for proliferation (phosphoinositide-3 kinase–Akt/ protein kinase B, Wnt, and Ras/Raf/mitogen-activated kinase signalling pathways, STAT3, Notch, and hepatocyte growth factor receptor signalling pathway), and finally, induction vascular endothelial growth factor expression [98, 102–105].

The majority of reports regarding association of urothelial cancer (both bladder and upper urinary tract) and BKV infection are case reports of immunocompromised patients [106–109]. It has to be emphasised that almost all of the described tumours are high-grade, highly aggressive with morphological features resembling the bladder cancers of SV40 transgenic mice (developed by the pathway of p53 and pRb inactivation) [98, 110, 111]. In a recent population-based study on 55 697 transplant recipients, the risk of bladder tumours was found to be 1.7-fold higher in patients treated for presumed BKV nephropathy compared with transplant recipients without prior BKV infection [112]. Similarly, a study on 2000 patients found a 12-fold elevated risk of bladder cancer in kidney transplant recipients with evidence of BKV-associated decay cells in urine, BK viremia, or biopsy-proven BKVN [113]. What is also worth mentioning, it is postulated that detection of BKV in bladder cancers from transplant recipients is more frequent than in bladder cancer in the general population [114]. Yet, some studies show a relatively high incidence of bladder carcinoma also in immunocompetent patients with cytological evidence of BK infection [115]. In case of prostate cancer, recent studies provide some evidence for a link between BKV infection/expression and cancer development not only in state of immuno-
suppression, but also in general population [116]. BKV particles are being found in cancerous cells, and moreover, in higher loads when compared with healthy tissue [117, 118]. Interestingly, BK virus was also more often observed in patients with lower Gleason scores. Additionally, BKV DNA was less frequently detected in overt, more advanced cancers which supports so called hit-and-run hypothesis (the virus activity paves the way for tumorigenic transformation only at early stages of the disease) [119]. What is worth revealing, in the study by Kaller et al., it was found that preoperative seropositivity to BKV LTag significantly reduced the risk of biochemical recurrence, independently of established predictors of biochemical recurrence such as tumour stage, Gleason score and surgical margin status [120]. However, it has to be remembered that available studies are burdened with many limitations and their findings do not provide any solid evidence for a relationship between BKV and prostate cancer. It is still unclear if there is any causative mechanism of BKV virus for prostate cancer and conclusions should be careful [121].

When kidney cancer is analysed, the incidence seems to not be clearly BKV – dependent [112]. Scarce case reports describe possible association, however, the case number is very low, and therefore, the conclusions should be drawn with caution [122, 123, 124].

CONCLUSIONS

The polyomaviruses are omnipresent in nature and the major sites of BK virus appearance are the kidney tubular epithelial cells and urinary bladder surface transitional cells. The virus usually stays latent, however, its replication may become active in various clinical situations of impaired immunocompetence and produce graft and life threatening complications. Because of the fact, that both diagnosis and treatment of BKV induced toxicity are difficult, strict surveillance and early intervention are therefore recommended for transplant recipients.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

References

1. Moens U, Calvignac-Spencer S, Lauber C, et al. ICTV Virus Taxonomy Profile: Polyomaviridae. J Gen Virol. 2017; 98: 1159-1160.

2. Polyomaviridae Study Group of the International Committee on Taxonomy of V, Calvignac-Spencer S, Feltkamp MC, et al. A taxonomy update for the family Polyomaviridae. Arch Virol. 2016; 161: 1739-1750.

3. DeCaprio JA, Garcea RL. A cornucopia of human polyomaviruses. Nat Rev Microbiol. 2013; 11: 264-276.

4. Tan CS, Korahlik I. Progressive multifocal leukoencephalopathy and other disorders caused by JC virus: clinical features and pathogenesis. Lancet Neurol. 2010; 9: 425-437.

5. Ambalathingal GR, Francis RS, Smyth MJ, Smith C, Khanna R. BK Polyomavirus: Clinical Aspects, Immune Regulation, and Emerging Therapies. Clin Microbiol Rev. 2017; 30: 503-528.

6. Randhawa PS, Finkelstein S, Scantlebury V, et al. Human polyoma virus-associated interstitial nephritis in the allograft kidney. Transplantation. 1999; 67: 103-109.

7. Binet I, Nickeleit V, Hirsch HH, et al. Polyomavirus disease under new immunosuppressive drugs: a cause of renal graft dysfunction and graft loss. Transplantation. 1999; 67: 918-922.

8. Hirsch HH, Knowles W, Dickenmann M, et al. Prospective study of polyomavirus type BK replication and nephropathy in renal-transplant recipients. N Engl J Med. 2002; 347:488-496.

9. Ramos E, Drachenberg CB, Portocarrero M, et al. BK virus nephropathy diagnosis and treatment: experience at the University of Maryland Renal Transplant Program. Clin Transpl. 2002: 143-153.

10. Arthur RR, Shah KV, Baust SJ, Santos GW, Saral R. Association of BK viruria with hemorrhagic cystitis in recipients of bone marrow transplants. N Engl J Med. 1986; 315: 230-234.

11. Bedi A, Miller CB, Hanson JL, et al. Association of BK virus with failure of prophylaxis against hemorrhagic cystitis following bone marrow transplantation. J Clin Oncol. 1995; 13: 1103-1109.

12. Dropulic LK, Jones RJ. Polyomavirus BK infection in blood and marrow transplant recipients. Bone Marrow Transplant. 2008; 41: 11-18.

13. Hirsch HH, Steiger J. Polyomavirus BK. Lancet Infect Dis. 2003; 3: 611-623.

14. Friedman DP, Flanders AE. MR Imaging of BK virus encephalitis. AJNR Am J Neuroradiol. 2006; 27: 1016-1018.

15. Hix JK, Braun WE, Isada CM. Delirium in a renal transplant recipient associated with BK virus in the cerebrospinal fluid. Transplantation. 2004; 78: 1407-1408.

16. Hirsch HH. BK virus: opportunity makes a pathogen. Clin Infect Dis. 2005; 41: 354-360.

17. Elidemir O, Chang IF, Schecter MG, Mallory GB. BK virus-associated hemorrhagic cystitis in a pediatric lung transplant recipient. Pediatr Transplant. 2007; 11: 807-810.

18. Pinto M, Dobson S. BK and JC virus: a review. J Infect. 2014; 68 Suppl 1:S2-8.

19. Gardner SD, Field AM, Coleman DV, Hulme B. New human papovavirus (B.K.) isolated from urine after renal transplantation. Lancet. 1971; 1: 1253-1257.

20. Lecatsas G, Prozesky OW, van Wyk J, Els HJ. Papova virus in urine after renal transplantation. Nature. 1973; 241: 343-344.

21. Coleman DV, Mackenzie EF, Gardner SD, et al. Human polyomavirus (BK) infection.
and ureteric stenosis in renal allograft recipients. J Clin Pathol. 1978; 31: 338-347.

22. Gardner SD, MacKenzie EF, Smith C, Porter AA. Prospective study of the human polyomaviruses BK and JC and cytomegalovirus in renal transplant recipients. J Clin Pathol. 1984; 37: 578-586.

23. Hogan TF, Borden EC, McBain JA, Padgett BL, Walker DL. Human polyomavirus infections with JC virus and BK virus in renal transplant patients. Ann Intern Med. 1980; 92: 373-378.

24. Boothpur R, Brennan DC. Human polyoma viruses and disease with emphasis on clinical BK and JC. J Clin Virol. 2010; 47: 306-312.

25. Egli A, Infanti L, Dumoulin A, et al. Prevalence of polyomavirus BK and JC infection and replication in 400 healthy blood donors. J Infect Dis. 2009; 199: 837-846.

26. Toan PQ, Bao Quyen LT, Thu Hang DT, et al. BK virus: Current understanding of pathogenicity and clinical disease in renal transplantation. J Med Virol. 1993; 41: 232-240.

27. Olsen GH, Hirsch HH, Rinaldo CH. BK virus in renal transplant patients. N Engl J Med. 1980; 302: 527-530.

28. Rogers DL, McClure GB, Ruiz JC, Abee CR, Slusher JEK, Alcendor DJ. BK Virus Replication in the Glomerular Vascular Unit: Implications for BK Virus Associated Nephropathy. Viruses. 2019; 11.

29. Shah KV, Daniel RW, Warszawski RM. High prevalence of antibodies to BK virus, an SV40-related papovavirus, in residents of Maryland. J Infect Dis. 1973; 128: 784-787.

30. Shah KV, Daniel RW, Warszawski RM. High prevalence of antibodies to BK virus, an SV40-related papovavirus, in residents of Maryland. J Infect Dis. 1973; 128: 784-787.

31. Shinohara T, Matsuda M, Cheng SH, et al. BK virus infection of the human urinary tract. J Med Virol. 1993; 41: 301-305.

32. Popik W, Khatua AK, Fabre NF, Hildreth JEK, Alcendor DJ. BK Virus Replication in the Glomerular Vascular Unit: Implications for BK Virus Associated Nephropathy. Viruses. 2019; 11.

33. Fishman JA. BK virus nephropathy-polyomavirus adding insult to injury. N Engl J Med. 2002; 347: 527-530.

34. Bressollette-Bodin C, Coste-Burel M, Hourmant M, et al. A prospective longitudinal study of BK virus infection in 104 renal transplant recipients. Am J Transplant. 2005; 5: 1926-1933.

35. Sawinski D, Goral S. BK virus infection: an update on diagnosis and treatment. Nephrol Dial Transplant. 2015; 30: 209-217.

36. Schmid H, Burg M, Kretzler M, et al. BK virus associated nephropathy in native kidneys of a heart allograft recipient. Am J Transplant. 2005; 5: 1562-1568.

37. Vigil D, Konstantinov NK, Barry M, et al. BK nephropathy in the native kidneys of patients with organ transplants: Clinical spectrum of BK infection. World J Transplant. 2016; 6: 472-504.

38. Schwarz A, Mengel M, Haller H, Niedermeyer J. Polyoma virus nephropathy in native kidneys after lung transplantation. Am J Transplant. 2005; 5: 2582-2585.

39. Ali FN, Meehan SM, Pahl E, Cohn RA. Native BK viral nephropathy in a pediatric heart transplant recipient. Pediatr Transplant. 2010; 14: E38-41.

40. Lorica C, Bueno TG, Garcia-Buitrago MT, Rusconi P, Gonzalez IA. BK virus nephropathy in a pediatric heart transplant recipient. Pediatr Transplant. 2010; 14: E38-41.

41. Verghese PS, Finn LS, Englund JA, Sanders JE, Hingorani SR. BK nephropathy in pediatric hematopoietic stem cell transplant recipients. Pediatr Transplant. 2009; 13: 913-918.

42. Wang RX, Li YJ, Lee WC, et al. The association between polyomavirus BK strains and BKV viruria in liver transplant recipients. Sci Rep. 2016; 6: 28491.

43. Inamoto Y, Lee SJ. Late effects of blood and marrow transplantation. Haematologica. 2017; 102: 614-625.

44. Filler G, Licht C, Haig A. Native kidney BK virus nephropathy associated with acute lymphocytic leukemia. Pediatr Nephrol. 2013; 28: 979-981.

45. Dekeyser M, Francois H, Beaudreuil S, Durrbach A. Polyomavirus-Specific Cellular Immunity: From BK-Virus-Specific Cellular Immunity to BK-Virus-Associated Nephropathy? Front Immunol. 2015; 6: 307.

46. Jiang M, Abend JR, Johnson SF, Imperiale MJ. The role of polyomaviruses in human disease. Virology. 2009; 384: 266-273.

47. Bohl DI, Storch GA, Rychlewitsch C, et al. Donor origin of BK virus in renal transplantation and role of HLA C7 in susceptibility to sustained BK viremia. Am J Transplant. 2005; 5: 2213-2221.

48. Hirsch HH, Yakhontova K, Lu M, Manzetti J. BK Polyomavirus Replication in Renal Tubular Epithelial Cells Is Inhibited by Sirolimus, but Activated by Tacrolimus Through a Pathway Involving FKBP-12. Transplant Proc. 2016; 48: 821-832.

49. Gonzalez S, Escobar-Serna DP, Suarez O, et al. BK Virus Nephropathy in Kidney Transplantation: An Approach Proposal and Update on Risk Factors, Diagnosis, and Treatment. Transplant Proc. 2015; 47: 1777-1785.

50. Hariharan S. BK virus nephritis after renal transplantation. Kidney Int. 2006; 69: 655-662.

51. Hogan TF, Padgett BL, Walker DL, Borden EC, McBain JA. Rapid detection and identification of JC virus and BK virus in human urine by using immunofluorescence microscopy. J Clin Microbiol. 1980; 11: 178-183.

52. Nickeleit V, Singh HK, Randhawa P, et al. The Banff Working Group Classification of Definitive Polyomavirus Nephropathy: Morphologic Definitions and Clinical Correlations. J Am Soc Nephrol. 2018; 29: 680-693.

53. Hirsch HH, Randhawa PS, Practice ASTIDCo. BK polyomavirus in solid organ transplantation-Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant. 2019; 33: e13528.

54. Marchetti S, Graffeo R, Siddu A, et al. BK virus DNA detection by real-time polymerase chain reaction in clinical specimens. New Microbiol. 2007; 30: 119-126.

55. Bechert CJ, Schnadig VJ, Payne DA, Dong J. Monitoring of BK viral load in renal allograft recipients by real-time PCR assays. Am J Clin Pathol. 2010; 133: 242-250.
56. Randhawa P, Ho A, Shapiro R, et al. Correlates of quantitative measurement of BK polyomavirus (BKV) DNA with clinical course of BKV infection in renal transplant patients. J Clin Microbiol. 2004; 42: 1176-1180.

57. Hirsch HH, Randhawa P, Practice ASTIDCo. BK polyomavirus in solid organ transplantation. Am J Transplant. 2013; 13 Suppl 4: 179-188.

58. Pang XL, Doucette K, LeBlanc B, Cockfield SM, Preiksaitis JK. Monitoring of polyomavirus BK virus viruria and viremia in renal allograft recipients by use of a quantitative real-time PCR assay: one-year prospective study. J Clin Microbiol. 2007; 45: 3568-3573.

59. Ding R, Medeiros M, Dadhania D, et al. Noninvasive diagnosis of BK virus nephritis by measurement of messenger RNA for BK virus VP1 in urine. Transplantation. 2002; 74: 987-994.

60. Bergallo M, Astegiano S, Sidoti F, et al. Real-time RT-PCR assay for the quantitation of polyomavirus BK VP1 mRNA levels in urine. Mol Biotechnol. 2010; 45: 82-86.

61. Drachenberg CB, Papadimitriou JC, Ramos E. Histologic versus molecular diagnosis of BK polyomavirus-associated nephropathy: a shifting paradigm? Clin J Am Soc Nephrol. 2006; 1: 374-379.

62. Celik B, Randhawa PS. Glomerular changes in BK virus nephropathy. Hum Pathol. 2004; 35: 367-370.

63. Nankivell BJ, Renthawa J, Sharma RN, et al. BK Virus Nephropathy: Histological Evolution by Sequential Pathology. Am J Transplant. 2017; 17: 2065-2077.

64. Schaub S, Hirsch HH, Dickenmann M, et al. Reducing immunosuppression preserves allograft function in presumptive and definitive polyomavirus-associated nephropathy. Am J Transplant. 2010; 10: 2615-2623.

65. Brennan DC, Agha J, Bohl DL, et al. Incidence of BK with tacrolimus versus cyclosporine and impact of preemptive immunosuppression reduction. Am J Transplant. 2005; 5: 582-594.

66. Ginevri F, Azzi A, Hirsch HH, et al. Prospective monitoring of polyomavirus BK replication and impact of pre-emptive intervention in pediatric kidney recipients. Am J Transplant. 2007; 7: 2727-2735.

67. Kidney Disease: Improving Global Outcomes Transplant Work G. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant. 2009; 9 Suppl 3: S1-155.

68. Drachenberg CB, Hirsch HH, Ramos E, Papadimitriou JC. Polyomavirus disease in renal transplantation: review of pathological findings and diagnostic methods. Hum Pathol. 2005; 36: 1245-1255.

69. Jouve T, Rostaing L, Malvezzi P. Place of mTOR inhibitors in management of BKV infection after kidney transplantation. J Nephropathol. 2016; 5: 1-7.

70. Almeras C, Fouloungue V, Garrigue V, et al. Does reduction in immunosuppression in viremic patients prevent BK virus nephropathy in de novo renal transplant recipients? A prospective study. Transplantation. 2008; 85: 1099-1104.

71. Costa C, Cavallo R. Polyomavirus-associated nephropathy. World J Transplant. 2012; 2: 84-94.

72. Vats A, Randhawa PS, Shapiro R. Diagnosis and treatment of BK virus-associated transplant nephropathy. Adv Exp Med Biol. 2006; 577: 213-227.

73. Zaman RA, Ettinger RB, Cheam H, Malekzadeh MH, Tsai EW. A novel treatment regimen for BK viremia. Transplantation. 2014; 97: 1166-1171.

74. Jordan SC, Toyoda M, Kahwaji J, Vo AA. Clinical aspects of intravenous immunoglobulin use in solid organ transplant recipients. Am J Transplant. 2011; 11: 196-202.

75. Williams JW, Javaid B, Kadambi PV, et al. Leflunomide for polyomavirus type BK nephropathy. N Engl J Med. 2005; 352: 1157-1158.

76. Lee BT, Gabardi S, Grafals M, et al. Efficacy of levofloxacin in the treatment of BK viremia: a multicenter, double-blinded, randomized, placebo-controlled trial. Clin J Am Soc Nephrol. 2014; 9: 583-589.

77. Anwar S, Brennan DC. Treatment of BK viremia after renal transplantation: are fluoroquinolones a false dawn? Clin J Am Soc Nephrol. 2014; 9: 445-447.

78. Sener A, House AA, Jevnikar AM, et al. Intravenous immunoglobulin as a treatment for BK virus associated nephropathy: one-year follow-up of renal allograft recipients. Transplantation. 2006; 81:117-120.

79. Garofalo M, Pisani F, Lai Q, et al. Viremia Negativization After BK Virus Infection in Kidney Transplantation: A National Bicentric Study. Transplant Proc. 2019; 51:2936-2938.

80. Sharma BN, Li R, Bernhoff E, Gutteberg TJ, Rinaldo CH. Fluoroquinolones inhibit human polyomavirus BK (BKV) replication in primary human kidney cells. Antiviral Res. 2011; 92:115-123.

81. Sharma BN, Marschall M, Henriksen S, Rinaldo CH. Antiviral effects of artesunate on polyomavirus BK replication in primary human kidney cells. Antimicrob Agents Chemother. 2014; 58: 279-289.

82. Cavallo R, Costa C, Bergallo M, et al. A case of ureteral lesions in a renal transplant recipient with a co-infection of BK virus and JC virus. Nephrol Dial Transplant. 2007; 22: 1275.

83. Gaston KE, Gabriel DA, Lavelle JP. Rare cause of ureteral obstruction. Urology. 2005; 66: 1110.

84. Rajpoot DK, Gomez A, Tsang W, Shanberg A. Ureteric and urethral stenosis: a complication of BK virus infection in a pediatric renal transplant patient. Pediatr Transplant. 2007; 11: 433-435.

85. Wingate JT, Brandenberger J, Weiss A, Scevola LG, Kuhr CS. Ureteral stent duration and the risk of BK polyomavirus viremia or bacteriuria after kidney transplantation. Transpl Infect Dis. 2017; 19.

86. Thomas A, Dropulic LK, Rahman MH, Geetha D. Ureteral stents: a novel risk factor for polyomavirus nephropathy. Transplantation. 2007; 84: 433-436.

87. Hashim F, Rehman S, Gregg JA, Dharnidharka VR. Ureteral Stent Placement Increases the Risk for Developing BK Viremia after Kidney Transplantation. J Transplant. 2014; 2014: 459747.

88. Kayler L, Zendejas I, Schain D, Magliocca J. Ureteral stent placement and BK viremia in kidney transplant recipients. Transpl Infect Dis. 2013; 15: 202-207.

89. Sencer SF, Haake RJ, Weisdl DJ. Hemorrhagic cystitis after bone marrow transplantation. Risk factors and complications. Transplantation. 1993; 56: 875-879.
122. Dao M, Pecriaux A, Bessede T, et al. BK virus-associated collecting duct carcinoma of the renal allograft in a kidney-pancreas allograft recipient. Oncotarget. 2018; 9: 15157-15163.

123. Dufek S, Haitel A, Muller-Sacherer T, Aufricht C. Duct Bellini carcinoma in association with BK virus nephropathy after lung transplantation. J Heart Lung Transplant. 2013; 32: 378-379.

124. Neirynck V, Claes K, Naesens M, et al. Renal cell carcinoma in the allograft: what is the role of polyomavirus? Case Rep Nephrol Urol. 2012; 2: 125-134.