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BK VIRUS NEPHROPATHY IN KIDNEY TRANSPLANTATION (LITERATURE REVIEW)

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The article presents a review of the literature on the current problem of modern transplantology – BK viral nephropathy after nephrotransplantation. Risk factors for BK virus reactivation in immunocompromised patients are reflected. The issues of screening and diagnosis of BK viral infection in people with a transplanted kidney are considered. The role of BK viral nephropathy in renal graft loss is emphasized. The clinical manifestations and treatment strategies of BK viral nephropathy in kidney transplantation are discussed.

Keywords: BKV, polyomavirus, kidney transplantation, BK viral nephropathy, diagnosis, treatment.

INTRODUCTION

BK virus (BKV, also known as polyomavirus) is a small non-enveloped virus with a circular, double-stranded DNA that belongs to the Polyomaviridae family. Its strains are classified into six genotypes according to the VP1 and NCCR polymorphisms. The four classified genotypes of BKV result in predominantly asymptomatic infections in childhood [1, 2]. Viral agnoprotein plays a key role in the BKV infectious cycle – in the assembly, morphogenesis and release of virions. About 80–90% of the population is seropositive for BKV. The main transmission routes are contact with mucous membranes, including the oral cavity, gastrointestinal tract, and respiratory tract [3]. After primary viremia, BKV remains in the kidney and uroepithelial cells, mainly in the parietal epithelium of Bowman's capsule, renal tubular epithelium and transitional epithelium, where it persists for a long time [4, 5]. BKV is capable of forming 40–45 nm intranuclear inclusion bodies in neuroepithelial cells of nephron tubules. Other localizations of latent BKV infection include the prostate, testicles, seminal tubules, cervix, vulva, and hematolymphoid tissues (peripheral blood mononuclear cells and tonsils) [6].

The virus is periodically reactivated and excreted with urine, but the infection remains asymptomatic in immunocompetent patients. Latent BK infection can become active when the functional activity of cellular immunity decreases against the background of immunosuppressive therapy or immunodeficiency states. BK infection has drawn increasing attention in recent decades due mostly to BKV-associated nephropathy (tubulointerstitial nephritis) resulting from profoundly compromised immune system [5, 7, 8]. BKV was first detected in 1971 in a renal transplant recipient with ureteral stricture. The first biopsy-confirmed case of BKV nephropathy was reported in 1993. It is debatable whether the rise in BKV incidence in subsequent years was the result of increased availability of reliable testing techniques for this infection or a consequence of the use of stronger immunosuppressive therapy regimens after kidney transplantation (KT). Because BKV-associated nephropathy (BKVN) frequently results in transplant rejection in patients, it is practically important to research its peculiarities. The final stage of kidney damage by BKV is characterized by interstitial fibrosis and tubular atrophy, accompanied by progressive nephron loss, impaired renal graft function and decreased graft survival [9].

In the first years after it has been reported, BKV nephropathy caused graft rejection in 50–100% of cases. However, as the role of BKV in posttransplant complications was recognized, the incidence of BKV-associated graft loss significantly decreased to 1–10%, although the 1-year incidence of graft loss ranges from 30% to 65% [10–12]. According to a recent study by Thorndyke et al (2023), the post-KT incidence of BKV nephropathy was 17.6%, with an 8.8% incidence of coinfection with cytomegalovirus [13]. Although BKV nephropathy is primarily seen in renal transplant recipients, cases have been reported in the kidneys of individuals with severe immunodeficiency [14, 15].

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The **objective** of the study is to examine current literature sources and summarize information about the nephrotoxic effects of immunosuppressive therapy.

MATERIALS AND METHODS

Scholarly articles in Russian and English dedicated to the issues of BKVN following KT were found using the search databases of Pubmed, Elsevier, Springer, and Elibrary. The search depth was 2017–2023. Keywords such as BKV, polyomavirus, kidney transplantation, BK viral nephropathy, diagnosis, and treatment were used in the search. The review included retrospective, prospective, analytical, descriptive studies, clinical guidelines, dissertation papers, systematic reviews and meta-analyses providing information on the principles of managing patients with BKV nephropathy in a transplanted kidney. Exclusion criteria for the review included conference abstracts, letters to journal editors, and papers published before 2017. A total of 77 publications were included in the present analysis.

RISK FACTORS FOR BK VIRUS REPLICATION IN KIDNEY TRANSPLANTATION

Because cellular immunity is most suppressed in the first year after transplantation as a result of induction therapy, it is during this period that the risk of BKV replication is increased [16], with 54% of cases occurring within the first 2–6 months after transplantation [13, 17].

A systematic review and meta-analysis of 34 publications presented by B. Demey et al. (2018) reported that tacrolimus regimen, deceased donor, male recipient, history of previous transplant, age at transplantation, ureteral stent use, delayed graft function, and acute rejection episodes increased the risk of BKV viremia to varying extents [18].

Similar data were obtained in a study by Alonso et al. (2022), who found that male sex (odds ratio [OR], 4.226; 95% confidence interval [CI] 1.660–10.758, p = 0.002), age (OR, 1.047; 95% CI, 1.008–1.088; p = 0.018) and retransplant (OR, 4.162; 95% CI, 1.018–17.015; p = 0.047) were independent predictors of BK polyomavirus infection [19].

Another study analyzing the clinical and laboratory data of 195 renal transplant recipients showed that deceased donor, decreased levels of direct bilirubin and blood neutrophils were risk factors for BK infection activation [20].

The intensity of immunosuppression is considered a key factor linked to BKV replication in kidney transplant recipients [16, 21, 22]. Immunosuppressive medications are known to have varying levels of immunosuppression. Research suggests that tacrolimus is associated with a higher risk of BKV reactivation in mammals than cyclosporine and mTOR inhibitors [18, 23, 24]. Against the background of such therapy, the virus can reactivate, induce lysis of tubular epithelial cells and release BKV virions into the bloodstream, causing various tubular and interstitial lesions with subsequent severe complications.

Recipient characteristics that increase the risk of BKV-induced nephropathy include advanced age, diabetes, and specific HLA-C alleles [18, 22]. At the same time, McCaffrey et al. (2021) has reported that BK infection is associated with younger patient age before transplantation, along with the recipient's negative serostatus for cytomegalovirus [21].

On the donor side, factors such as reduced immune response to BKV and BK-viruria prior to transplantation contribute to virus reactivation [25].

Donor-recipient interactions: high-risk serologic status in BKV-positive and BKV-negative donors, ABO incompatibility, HLA mismatch, reduced graft function, rejection or ischemia of the transplanted kidney, and ureteral stent increase the risk of BKVN in a transplanted kidney [26].

Another potential risk factor for BKVN is congenital anomalies of the kidneys and urinary tract. According to Avcı et al. (2022), among children aged 0–18 years who received renal transplants, the incidences of congenital kidney and urinary tract anomalies were 30.3% and 66.6% in those without and with BK polyomavirus infection, respectively ($p < 0.05$) [27]. The incidence of cytomegalovirus infection was significantly higher in the BK polyomavirus-positive group than in the non-infected group ($p < 0.05$).

The pathogenesis of BKV infection is presented in Figure.

CLINICAL MANIFESTATIONS OF BK POLYOMAVIRUS-ASSOCIATED NEPHROPATHY

Clinically significant BK infection occurs in renal transplant recipients due to reactivation of latent infection or transmission of new infection from the donor kidney [28, 29]. Stages of BK infection include viruria, viremia, and allograft nephropathy [26]. Persistent viruria in immunocompetent individuals can progress to viremia, which is initially asymptomatic [30]. Compared to viruria, viremia has been found to be a more accurate indicator of BKVN [31, 32].

The prevalence of viremia and BKVN is 10–15% and 3–5%, respectively [33]. According to other reports, viruria and viremia are detected in about 30% and 12% of renal transplant recipients, respectively [1, 31]. In a study of 326 transplants including 246 patients, Bicalho et al. (2018) found that the prevalence of viruria was 36.9%, viremia was 22.3%, and nephropathy was 3.2% [34]. Nearly half of kidney transplant recipients develop viremia within 2–6 weeks of the onset of viruria, and a comparable percentage of patients who have viremia also experience BKVN within the same time period [31, 35]. There are reports that viremia affects 10–30% of recipi-

ents in the first 6 months following transplantation and in 5–10% of recipients thereafter [32, 36].

BKVN usually occurs after a period of sustained, progressively increasing viremia, which is characterized by impaired kidney function with or without urinary dysfunction. Ureteral stenosis and hemorrhagic cystitis are other manifestations of BKV, although they are less common in renal transplant recipients [37].

Given its prolonged persistence in the genitourinary epithelium, there has been discussion on a potential link between BKV and genitourinary malignancies in renal transplant recipients [38]. Animal and *in vitro* studies demonstrate that BKV causes oncogenesis and cell transformation [39]. However, findings are unclear since BKV nephropathy patients have reduced cellular immunity, which itself is a risk factor for malignant neoplasms.

SCREENING AND DIAGNOSTIC OPTIONS FOR BK VIRUS

Screening kidney recipients for BKV infection and renal dysfunction at 1, 3, 6, 9, 12 months after KT allows to reduce immunosuppressive medication and promptly assess the risk of BKV injury to the graft [28, 33, 40]. According to international guidelines, screening should be done monthly for the first 6 months after transplantation and then every 3 months for the next 18 months [1, 22, 41]. It should be noted that such screening tactics are cost-effective. Compared with no screening, the incremental benefits of screening were 0.294 life-years saved and 0.232 quality-adjusted life-years saved. Total savings from screening were A$6986 (US$5057) [42].

Following a reduction in immunosuppressant dosage, renal function, medication levels, and viral load should be monitored. High levels of BK viremia have been linked to higher incidence of BKVN and increased incidence of acute rejection and overall worse graft survival (OR 1.988; 95% CI 1.012–3.907; p = 0.046) [19]. However, with this modification to therapy regimen, the elevated risk of kidney transplant rejection should be considered.

BKV viral load is measured by polymerase chain reaction (PCR). Differences in DNA extraction methods, sample type/source, primer and probe sequences, and variation in BKV genotype all influence assay results [43–45]. The results of assays conducted in different laboratories may differ as a result of these factors [46].

BKV nephropathy should be suspected when the plasma BKV load is ≥10,000 copies/mL. According to Bicalho et al. (2018), the cut-off value of viremia that best discriminates the progression to sustained viremia and to BK polyomavirus-associated nephropathy was 37,488 and 44,956 copies/mL, respectively [34]. Based on analysis of 393 time-matched urine and plasma samples collected after KT, Brochot et al. (2019) identified a viruria threshold of 6.71 $\log_{10}$ copies/mL as the best threshold for diagnosing BKVN (sensitivity 90.9% (95% CI 86.5–95); specificity 90.3% (95% CI 86.3–94.3) [47].

Cytologic analysis is the most specific and easy method of examining urine sediment. Typical BKV-infected

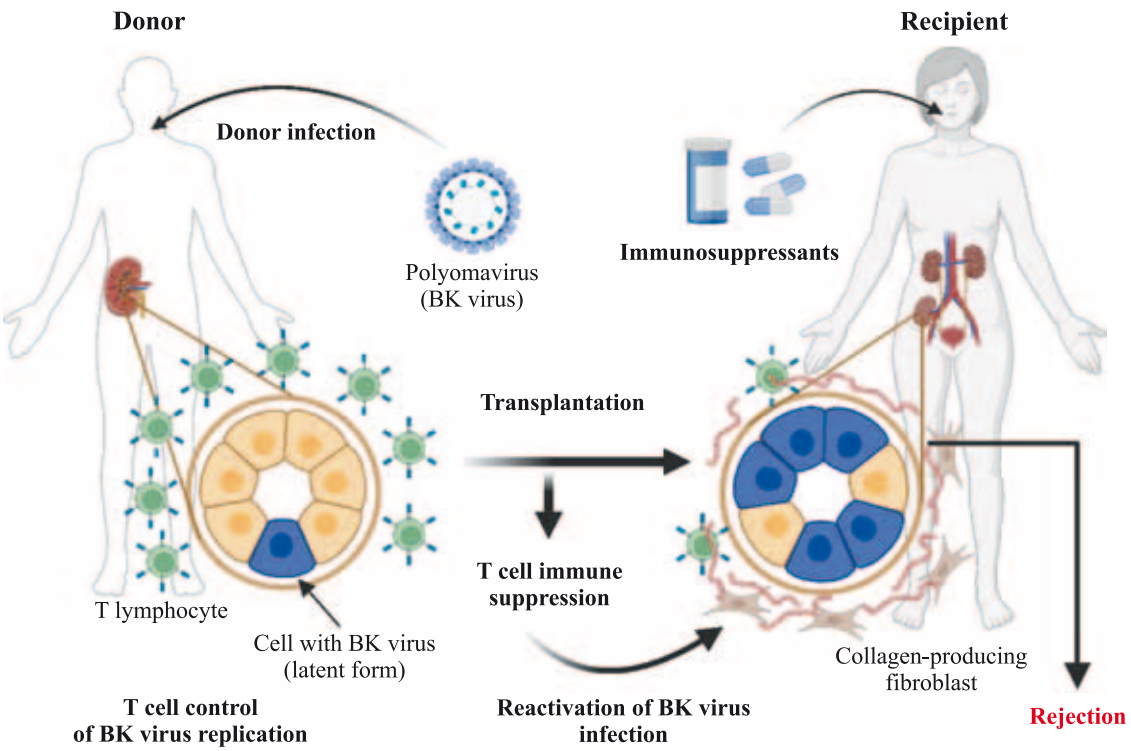

Fig. Pathogenesis of BK virus infection and its induced nephropathology in kidney recipients. The figure was prepared using online program BioRender (www.biorender.com)

cells found in urine cytology are called decoy cells because of their similarity to renal carcinoma cells, which can make differential diagnosis challenging [48]. They are tubular epithelial or urothelial cells with ground-glass-like nuclear inclusions surrounded by a condensed chromatin rim. They may also have "owl's eye" inclusions, multinucleation, or clumped chromatin. Although trap cells are a marker of BKV replication, they do not necessarily indicate BKV infection, as false-positive results are possible in transplant patients [49]. Nevertheless, the absence of trap cells in urine cytologic examination has a high negative predictive value for diagnosis of BK infection [50].

Non-invasive markers of BK infection are cylinder-like aggregates of mature virions and Tamm–Horsfall protein (uromodulin), which can be detected in urine samples, for example, by negative-staining electron microscopy [51]. Their presence or absence has an extremely high positive and negative prognostic value for diagnosis of BKV nephropathy, and the amount of BK Haufen shedding correlates significantly with severity of the disease, degree of lysis of tubular epithelial cells, as well as presence of trap cells, viruria, and viremia in the urine [52].

Kant et al. (2020, 2021, 2022) evaluated the association of donor-derived cell-free DNA (dd-cfDNA), BK viral load in recipient plasma with biopsy results [53–55]. It is known that dd-cfDNA circulates in the recipient's bloodstream and can be quantified by droplet digital PCR after targeted multiplex pre-amplification. Higher levels of dd-cfDNA were shown to correlate with higher BK viral load as well as histological changes diagnosed at biopsy that met Banff criteria for T-cell-mediated rejection. The authors concluded that dd-cfDNA levels may be an informative noninvasive test to assess BKV progression to BKVN.

Renal allograft biopsy with confirmation of interstitial nephritis and viral-induced cytopathic changes is currently the gold standard for diagnosing BKVN. This procedure not only enables the diagnosis of BKVN but evaluates the severity of the viral lesion and the existence of other concomitant lesions [1, 22]. Biopsy is conducted when there is persistent viremia – two or more viremia above 10,000 copies/mL [34].

However, it could be challenging to confirm the presence of BKV histologically. When sampling from unaffected renal parenchyma, the random and focal nature of the infection, especially in the early stages, may lead to false-negative results. Since BKV is tropic to the kidney medulla, it is necessary that the biopsy specimen contains the medulla to minimize the likelihood of sampling error [56, 57]. According to some reports, BKVN is undetected in nearly 30% of cases where biopsy samples are taken incorrectly. If the initial biopsy does not confirm the presence of BKVN, but there are clinical manifestations of the disease, a follow-up biopsy is advised.

The histologic picture of BKVN is similar to that of acute transplant rejection, which makes early identification more challenging. In both cases, the key histological manifestations are tubular injury, tubulitis, and interstitial inflammation. These are regarded as acute cellular rejection when there are no additional morphological or immunohistochemical signs of BK infection [58]. Endarteritis, arterial fibrinoid necrosis, glomerulitis, or C4d staining of peritubular capillaries are among the signs of vascular injury that are typically more consistent with acute rejection than with polyomavirus infection [58]. According to Yang et al. (2022), high-frequency ultrasound can be used to differentiate between BK polyomavirus-associated nephropathy and renal graft rejection: the presence of eccentric hydronephrosis and subcapsular hypoechoic areas has a high specificity [59]. Undoubtedly, histologic data should be correlated with the history of the disease and the results of additional laboratory tests, primarily BKV load and the presence of donor-specific antibodies.

Auxiliary tests, such as immunohistochemical staining or *in situ* hybridization can be used to improve the accuracy of BKV diagnosis in biopsy specimens [57, 60]. Immunohistochemical staining enables the detection of BKV at early stages of infection, even before the development of characteristic cytopathic changes on conventional staining, and also allows differentiating BKV from other viral nephropathies observed in immunocompetent patients (adenovirus, cytomegalovirus infection, etc.). Detection of the large SV40 T-antigen (homologous to BKV polyomavirus Simian Virus 40) indicates active BKV replication, the amount of which reflects viral load. When evaluating staining with SV40 T antibodies, the reaction intensity is expressed as a score (0–3), and the percentage of tubules with cell staining (<1%, ≥1% and ≤10%, >10%) and the percentage of stained tubular cells are also taken into account [57].

Several grading systems have been proposed for assessing BKV severity; the Banff Working Group system is one of the most popular [57, 61]. The Banff Working Group Histological Classification for polyomavirus nephropathy is a three-level approach that takes into account the degree of morphological features of BK infection, the intensity of interstitial fibrosis, and the degree of viral load (Table).

Renal graft function is most impaired in class III patients and their prognosis is significantly worse.

Thus, characteristic cytopathic changes and positive immunohistochemical tests using antibodies specifically directed against BKV or against the cross-reactive large SV40 T antigen must be present for a conclusive diagnosis of BKV-induced nephropathy in a transplanted kidney [62]. Research on potential biomarkers of BKVN in a kidney transplant appears to be relevant and valuable.

Table

Banff Working Group Histological Classification for polyomavirus nephropathy [61]

Classes of polyomavirus nephropathy					
Class I		Class II		Class III	
pvl	Banff ci score	pvl	Banff ci score	pvl	Banff ci score
1	0–1	1	2–3	–	–
–	–	2	0–3	–	–
–	–	3	0–1	3	2–3

Note: pvl denotes the polyomavirus replication/load level, calculated as follows: pvl1: ≤1% of all tubules/ducts with polyomavirus replication; pvl2: from >1 to ≤10% of all tubules/ducts with polyomavirus replication; pvl3: >10% of all tubules/ducts with polyomavirus replication; Ci denotes interstitial fibrosis: Ci0: interstitial fibrosis in ≤5% of the cortex; Ci1 denotes interstitial fibrosis in >5% and ≤25% of the cortex; Ci2 denotes interstitial fibrosis in >25% and ≤50% of the cortex; Ci3 denotes interstitial fibrosis in >50% of the cortex.

APPROACHES TO THE TREATMENT OF BKVN, INCLUDING IN TRANSPLANTED KIDNEY

Reducing the immunosuppression intensity while keeping an eye on the viral load in urine and/or blood is a fundamental principle in the treatment of BK-viremia and BKVN, although it is associated with the risk of acute rejection after treatment [22, 63, 64]. To lessen immunosuppression, the following strategy has been suggested [16]:

1. Cutting the immunosuppressive dosage by half against the background of previous doses of calcineurin inhibitor and/or prednisolone, while checking serum creatinine and viral load levels by plasma PCR in the same laboratory every 2 weeks.
2. If BK viral load stays the same or rises, the immunosuppressants should be discontinued completely.
3. If the viral load does not decrease within 4 weeks despite discontinuing the immunosuppressant (4–6 ng/mL for tacrolimus and 50–100 ng/L for cyclosporine), a reduction in calcineurin inhibitor target values is recommended.

Quinolones, cidofovir, leflunomide, and intravenous immunoglobulin are additional therapies for BKV infection [16]. It should be noted that among these medications, only intravenous immunoglobulin has an evidence base for efficacy against BKV infection [65–67].

Intravenous immunoglobulin is given where maximum reduction of immunosuppression fails [65]. This treatment strategy is justified by the fact that intravenous immunoglobulin preparations contain BKV-neutralizing antibodies [68]. In a pediatric population of kidney recipients on the background of intravenous immunoglobulin treatment, Mohammad et al. (2022) reported that viral resolution was achieved in 70% and that no difference was noted in estimated glomerular filtration rate between BKV and non-BKV group (p = 0.438). There were no rejection episodes and graft survival was 100% over median follow-up of 3 years [69].

Although quinolones (ciprofloxacin and levofloxacin) have been shown to have antiviral qualities *in vitro*, there is no convincing evidence to support their efficacy in preventing and treating BK virus infection following transplantation [70].

Although cidofovir, a cytosine nucleotide analog, has shown action against polyomaviruses *in vitro* [71], subsequent studies have demonstrated no benefit from cidofovir use. Moreover, cidofovir has been linked to proteinuria, proximal tubular dysfunction, and impaired renal function [72].

Teriflunomide (A771726), an active metabolite of the prodrug leflunomide, exhibits antiviral and immunosuppressive qualities. Despite initial enthusiasm for its use in BKV infection [73], the efficacy of leflunomide in BKVN is still debatable [74].

In the absence of developed and implemented antiviral agents with activity against BKV, the potential use of individually selected phytotherapeutic agents with antiviral properties should be considered. For example, San-Yuan Chen et al. (2017) found that extracts of *Rhodiolae Kirliowii Radix et Rhizoma* and *Crataegus pinnatifida* fruits inhibited BKV cell infection, as evidenced by reduced expression of viral proteins VP1 in BKV-infected renal epithelial HK-2 cells. The calculated 50% effective doses against BKV were 21.68 μg/mL for *Rhodiolae Kirliowii* extract and 65.54 μg/mL for *Crataegus pinnatifida* extract. The cytotoxicity study showed that at concentrations of 300 μg/mL, the studied extracts did not harm kidney cells [75].

Patients with BKVN-associated graft loss should be considered for re-transplantation, given the strong evidence supporting its effectiveness, [76, 77]. One-year allograft survival in BKVN patients who undergo re-transplantation is 91% [76].

CONCLUSION

BKV infection continues to be one of the most common clinical challenges in transplantology. There are numerous risk factors for BKV reactivation. Posttransplant monitoring of BKV reactivation, which should include searching for “trap cells” in urine and assessing viremia by PCR is the cornerstone of BKVN prophylaxis. BKVN treatment is an unsolved problem since the key aspect is to reduce immunosuppression, which may lead to graft rejection. Antiviral medications designed to destroy BKV have not yet been used in clinical settings.

The authors declare no conflict of interest.

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