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REVIEW ARTICLE

BK polyomavirus (BKPyV) infection in renal transplantation: viral characteristics, diversity, reactivation, risk factors and laboratory diagnosis

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Summary

BK polyomavirus (BKPyV) is a ubiquitous human polyomavirus. Following primary infection, which is usually asymptomatic, BKPyV establishes lifelong persistence in renal epithelial cells. In recent years, the use of potent immunosuppressive drugs after transplantation has led to an increasing incidence of BKPyV reactivation in patients with organ transplants, placing BKPyV among the major risk factors for graft loss in kidney transplant recipients. This review provides an overview of BKPyV infection in the context of renal transplantation from a virologist's perspective. The first part of the review covers basic virology, including virion structure, genome organization, life cycle, mechanisms of lifelong BKPyV persistence, and basic epidemiology. The meeting points of basic and clinical virology are explained through BKPyV diversity and its clinical implications. The clinical aspects are discussed, including donor- and recipient-related risk factors for BKPyV reactivation, the clinical importance of BKPyV subtyping, and serotype-specific immunity. In the second part of the review, emphasis is placed on the possibilities of laboratory diagnostics of BKPyV infection. Finally, the review provides current international recommendations for screening and monitoring of BKPyV infection in the post-transplant period. By integrating virological, clinical, and diagnostic aspects, this review highlights the complexity of BKPyV infection after kidney transplantation, underscoring the need for optimized monitoring strategies, further research into the clinical significance of viral diversity, and improvements in therapeutic protocols to control BKPyV infection.

Keywords: BK polyomavirus, BKPyV, polyomavirus-associated nephropathy, risk factors, kidney transplantation

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INTRODUCTION

According to the American and European Nephrology Associations, approximately 850 million people worldwide currently have some form of kidney disease (1). Kidney transplantation is considered the most effective therapy for patients with end-stage kidney disease (1). Currently, about one and a half million people with end-stage kidney disease are waiting for a transplant, with that number increasing by about 120,000-150,000 annually (1). Over the last decade, significant progress has been made in renal transplantation, with a 5-year patient survival rate of over 90% (1). However, rapid development and use of potent immunosuppressive drugs have led to an increased incidence of various infections in recent years, placing infection among the major risk factors for graft loss in patients with organ transplants (2). BK polyomavirus (BKPyV) was first identified in 1971 in the urine of a Sudanese kidney transplant patient with the initials B.K., who developed urethral stenosis (3). Ever since, BKPyV infection in kidney transplant recipients has become a major contributor to graft loss, associated with the development of polyomavirus-associated nephropathy (4).

Considering the rapid, aggressive onset of BKPyV infection in transplant patients, coupled with the lack of effective antiviral therapy, this presents a major challenge for clinicians regarding timely diagnosis, prevention, and treatment.

METHODS

A PubMed search was conducted to identify studies on BKPyV virion structure and life cycle, reactivation, epidemiology, risk factors, renal transplantation, and laboratory diagnosis. Only articles published in English were included.

BKPyV structure

BKPyV is a small DNA virus that belongs to the *Polyomaviridae* family. The non-enveloped virion is 45 nm in diameter and has icosahedral capsid symmetry, enveloping the circular double-stranded DNA (dsDNA) genome (5). The major virion protein is viral protein 1 (VP1), which accounts for almost 80% of the virus's protein composition and is composed of 72 pentamers (6). The BKPyV genome is approximately 5000 bp and consists of two coding regions: the early and late coding regions, separated by a noncoding control region (NCCR). The products of early genes located within the early coding region are the following nonstructural proteins: large T antigen (TAg), small T antigen (tAg), and truncated T antigen (Tag) (7). Transcription of late genes within the late coding region leads to the synthesis of the structural proteins VP1, VP2, VP3, and the agnoprotein.

There are two forms of the BKPyV NCRR: the archetype and the rearranged form (variant). The archetype variant is the dominant form in urine samples (8). This form enables the virus to transmit and circulate within the human population; hence, it is called transmissible (8). This variant consists of five blocks OPQRS with fixed nucleotide numbers (8). The rearranged form of the NCRR is most commonly detected in the kidneys, blood, and other organs of patients with a BKPyV-associated disease (9). Deletions, duplications, insertions, or substitutions within the NCRR blocks of the archetype form create the rearranged variants. *Gossert et al.* (10) showed that BKPyV with a rearranged NCRR is present in kidney transplant patients. These forms are more often detected in blood than in urine and are associated with higher rates of viral replication in blood and greater cytocidal potential (10). There is limited data from Serbia regarding polyomavirus NCRR variability among immunocompromised and healthy individuals (11-12). Still, in a small sample size of polyomavirus-positive isolates from Serbia, NCRR variability was detected (11-12).

Products of the early coding region of the BKPyV genome, TAg and truncTAg, are predominantly nuclear in infected cells due to a nuclear localization signal (13). The N-terminal part of both proteins is necessary for viral replication and interacts with heat shock proteins (13-14). On the other hand, small tAg is found in both the nucleus and cytoplasm, and its role is to downregulate viral DNA replication (14-15).

Among the products of the late coding region of the BKPyV genome, VP1 consists of five loops, designated BC, DE, EF, GH, and HI (16). VP1 is the main structural protein that builds the outer part of the capsid (7). In addition to its role in virion formation, VP1 also plays a role in the binding of the virus to receptors on target cells. The receptor binding site is located within the BC and HI loops of VP1 (16). Within the BC loop, there is also a BKPyV typing region, used to classify BKPyV isolates into subtypes and subgroups (17). Mutations in VP2 and VP3 reduce viral infectivity by 99% compared to the wild-type virus, indicating that these proteins are crucial for virion formation (18). Agnoprotein is a protein consisting of 66 amino acids and is localized in the cytoplasm and nucleus during the BKPyV life cycle (19). Agnoprotein is involved in the processes of morphogenesis, maturation, and/or virus release from the infected cell (19).

Several polyomaviruses, including BKPyV, have been shown to synthesize microRNA (miRNA) (20, 21). MiRNAs are noncoding RNAs of 20 to 22 nucleotides in length, transported from cell to cell, and interfere with both viral and cellular gene expression (22). The main role of miRNAs is to silence genes in noninfected cells during viral infection, thereby affecting the host's immune response and contributing to viral persistence (22). BKPyV miRNAs have also been demonstrated in patients with BKPyV-associated disease (7). Infection

with the BKPyV archetype variant leads to the production of large quantities of miRNA that inhibit viral DNA replication (23). On the other hand, infection with rearranged forms leads to insufficient miRNA production, preventing them from reducing the levels of early mRNAs, resulting in a higher rate of viral replication of the rearranged BKPyV form (23).

BKPyV life cycle

The first step in the BKPyV life cycle is the binding of VP1 to cell receptors such as glycoproteins with α(2,3)-sialic acid and gangliosides GT1a and GD1a (24, 25), followed by cell entry via receptor-mediated endocytosis (26). Using host cytoskeletal machinery, vesicles containing BKPyVs are transported to the endoplasmic reticulum (ER), where partial decapsidation and release into the cytosol are initiated (27). The BKPyV genome contains nuclear localization signals within VP2 and VP3; host cell importins (alpha and beta) bind to them and escort the genome to its final destination. In this host nucleus, transcription of viral genes and viral genome replication takes place (28).

In the nucleus, transcription of the early viral genes, the large T and small t antigens, occurs. Large TAg binds to the origin of replication (*ori*) within the NCRR and, with its helicase activity, first leads to unwinding of double-stranded DNA, then binds to cellular proteins necessary for viral replication, such as DNA polymerase, topoisomerase I and II (7). Multifunctional large TAg alters the cellular microenvironment and drives cells into S phase, providing the most favorable conditions for viral genome replication (7). DNA replication occurs continuously in the 5'-3' direction and via Okazaki fragments in the 3'-5' direction. Upon synthesis of new viral genome copies, TAg suppresses the transcription of early genes and induces the transcription of late viral genes VP1, VP2, VP3, and agnoprotein. The synthesis of early and late proteins takes place in the cytoplasm on ribosomes. Both early and late proteins contain nuclear localization signals that direct them to the nucleus, where they perform their functions (27). Through the process of self-assembly, an icosahedral capsid of the BKPyV is formed, and viral DNA is incorporated (29). Newly formed virions leave the cell either by lysis or secretion (18).

Epidemiology and BKVPyV persistence

Primary BKPyV infection usually occurs in early childhood. According to data, BKPyV seroprevalence varies significantly by age. In children aged 6-9 years, BKPyV seroprevalence reaches 90%, and this seroprevalence is maintained until 40 years, after which a slow decline is observed, reaching 68% at 60-69 years (30). The most common entry route is the respiratory tract, but transmission is also possible via the feco-oral route, blood transfusion, and transplacentally (31). Primary infection is usually asymptomatic or presents as a mild respiratory disease. Upon initial replication at the entry site, BKPyV disseminates via the bloodstream to secondary infection sites, including the kidneys (31-33). After primary infection, BKPyV establishes lifelong persistence in kidney epithelial cells, with occasional asymptomatic viruria in immunocompetent patients.

In contrast, in immunosuppressed patients, reactivation is much more frequent and significant, and in addition to viruria, viremia also occurs (32-36). BKPyV DNA has also been detected in other cells and tissues such as lymphocytes, brain, and lymph nodes (37-38). The exact mechanisms by which BKPyV establishes persistence, as well as the factors and conditions that drive reactivation in immunocompromised patients, remain to be fully clarified. What is known is that BKPyV miRNA plays a role in persistence by regulating viral replication. *Broekema and Imperiale* (23) showed increased miRNA expression complementary to the 3' end of the large T antigen mRNA, which self-limits the replication of the archetype variant, leading to lifelong persistence and latency of BKPyV. Other mechanisms of persistence have not yet been proven, and further research in this direction is necessary.

BKPyV subtypes and clinical importance of viral diversity

The role of BKPyV diversity in the development and outcomes of different BKPyV-associated diseases remains unclear. In a review by *Moens and Van Ghelue* (39), numerous amino acid substitutions were described in VP1, large TAg, and agnoprotein; however, the biological consequences of these changes remain unknown. Polymorphisms within the coding region and the NCRR of the BKPyV genome can alter the permissiveness of target host cells. The diversity of BKPyV will certainly contribute to the development of antiviral resistance if specific drugs for the treatment of BKPyV-associated diseases are developed in the near future.

BKPyV isolates are classified into four subtypes (I-IV) based on polymorphisms in the VP1 gene region (nc. positions 1744-1812), which encodes amino acids 63-81 of the VP1 protein (17). Subtype I is widespread worldwide (more than 80% of sequenced isolates), followed by subtype IV (about 15% of sequenced isolates), which predominates in East Asia and Europe. In contrast, subtypes II and III are rarely detected among BKPyV isolates worldwide (40-42). Based on phylogenetic analysis, four subgroups (Ia, Ib1, Ib2, and Ic) are distinguished within subtype I, and within subtype IV, six subgroups (IVa1, IVa2, IVb1, IVb2, IVc1, IVc2) (41-44). Based on available scientific data in Serbia regarding BKPyV subtype distribution, the most dominant subtype is I, followed by IV, in both immunocompromised and immunocompetent individuals (11).

Do certain subtypes of BKPyV have a greater potential to cause BKPyV-associated diseases compared to

other subtypes? Recent studies indicate that different BKPyV subtypes differ in tropism and pathological potential, as well as in replication rates within the same cells (45-46). The BKPyV subtype I replicates more rapidly and more efficiently in human renal epithelial cells than subtype IV (47). In kidney transplant recipients, higher BKPyV DNA viruria levels were detected in subtype Ia than in subtype Ib1 (48). In one study involving 19 grafts from nephrectomized patients with polyomavirus-associated nephropathy subtype I, BKPyV was identified as the cause of graft loss (40). Since the classification of BKPyV is based on single-nucleotide polymorphism, the question that arises is whether such small genetic alterations in the form of a few nucleotide changes can give such a biological advantage to certain subtypes of BKPyV compared to others. On the other hand, this may reflect the distribution of BKPyV subtypes/subgroups in the general population of a given geographic area (40).

Despite BKPyV having one of the highest mutation rates among DNA viruses, its diversity is poorly studied (49). The variability also exists within the NCRR. Over time, this variability leads to the emergence of quasispecies that can affect viral replicative capacity (50). Mixed infection with different BKPyV subtypes is also possible, and in one study, 12 of 25 patients had infections with multiple BKPyV subtypes (51). The recombination events during dual infections represent another form of viral evolution and have been detected among BKPyV isolates (51). Another interesting feature of BKPyV is the ability to detect different viral subtypes in the urine and blood of the same patient, suggesting tissue-specific selection pressure (52).

In addition, does the virulence of the donor virus matter, or is it a mismatch between the donor's viral subtype and the recipient's anti-BKPyV antibodies (53)? *Pastrana et al.* (45) showed that BKPyV subtypes/subgroups I, II, III, and IV are entirely different serotypes. Their study showed that in the serum of healthy volunteers, almost all had neutralizing antibodies against BKPyV subtype I, and most had no detectable neutralizing antibodies against BKPyV subtypes III and IV (45). They concluded that individuals infected with one BKPyV subtype lack humoral protection against other BKPyV subtypes (45). This conclusion represents worrying data because after transplantation, BKPyV infection is most often of donor origin (54). Also, kidney recipients without sufficient neutralizing antibody titers against BKPyV are at greater risk of BKPyV replication after transplantation (55). Results from other studies indicate that immunity to BKPyV is subtype-specific and, as such, significantly impacts BKPyV reactivation after kidney transplantation (53).

Reactivation of BKPyV in kidney transplant patients

Due to suppressed cellular immunity, with a peak in the first year after transplantation, viral reactivations/infections mostly occur during this period. In kidney transplant recipients, infections occur either as a result of reactivation of latent viral infections or *de novo* infection due to viral transmission via the donor kidney. Viruria or Decoy cells detection in urine occurs in 23-73% of kidney transplant patients, while BK viremia occurs in 8-62%, with the highest incidence 3 to 6 months after transplantation. The BKPyV-associated nephropathy most often occurs during the first post-transplantation year with an incidence of 1 to 10% (56-59).

The possible explanation for the wide range of BKPyV reactivation frequency lies in the use of different immunosuppressive therapy protocols across transplant centers, the frequency of BKPyV monitoring in kidney transplant patients, and the methodology and sensitivity of the tests used (60). Most BKPyV reactivations are clinically asymptomatic, and if symptoms are present, they generally indicate graft failure and a negative outcome (57). Because of all this, regular monitoring of BKPyV reactivation is common practice at most transplant centers worldwide. The definitive diagnosis of BKPyV-associated nephropathy requires a kidney biopsy, which is usually performed when persistent viremia exceeds 10,000 copies/mL or when there is evidence of altered allograft function (61).

In BKPyV-associated nephropathy (BKPyVAN), the cytopathogenic effects of the virus are manifested in tubular epithelial cells and are characterized by the presence of basophilic viral inclusions and nuclear enlargement (62). Also, there is significant tubular cell injury and associated intestinal inflammation that may lead to a misdiagnosis of acute renal rejection, especially during the resolution of BKPyVAN, when viral inclusions are less prominent (63). Persistent BKPyVAN leads to renal scarring with progressive tubular atrophy and intestinal fibrosis (62). BKPyVAN is classified into three stages based on the severity of changes observed on histopathological preparations, with more pronounced changes associated with higher viremia levels and lower graft survival (62).

Munoz-Gallego et al. (64) observed that kidney transplant patients infected with mixed BKPyV subtypes have an earlier onset of infection, higher viral loads, and are more often symptomatic. They also concluded that the presence of clinical manifestations is an independent predictive factor of a high BKPyV viral load (64). Patients with subtype I had a late onset of BKPyV reactivation, lower viral load, and were without clinical manifestations. Also, patients with subtype I more often had normal serum creatinine levels, whereas patients with subtype IV rarely did. Results of this study also confirmed that BKPyV viral load >10,000 copies/mL is the cut-off for significant viremia and consequent negative consequences in kidney transplant patients (64).

Other clinical manifestations of BKPyV reactivation include hemorrhagic cystitis and urethral stenosis,

which are rare in renal transplant patients and are most commonly seen in hematopoietic stem cell transplant patients. Also, there are studies linking BKPyV to the development of uroepithelial carcinoma in transplant patients, as patients who develop BKPyVAN have a reduced cellular immune response and, as a consequence, reduced surveillance of tumor development, leading to an increased risk of developing cancer (65). The T antigen of BKPyV plays a significant role in oncogenesis by inhibiting the tumor suppressor proteins RB and p53, leading to cell cycle entry and inhibition of apoptosis (66).

Risk factors for BKPyV reactivation

BKPyV reactivation ranks among the serious complications after kidney transplantation. Risk factors for BKPyV reactivation in kidney transplant patients can be divided into three groups: donor-related, recipient-related, and transplantation-related (61). The BKPyV serostatus of donors and recipients is an important risk factor for the development of BKPyV-associated nephropathy. The situation in which the donor has anti-BKPyV antibodies and the recipient is seronegative increases the risk of BK viremia by 10-fold and, consequently, the risk of polyomavirus-associated nephropathy and graft rejection (67-68). Furthermore, the titer of anti-BKPyV-specific antibodies is also associated with the risk of BKPyV replication in renal transplant patients (67-69). High anti-BKPyV IgG titers in donors and low anti-BKPyV IgG titers in recipients increase the risk of BKPyV reactivation (68). Also, *Verghese et al*. (70) showed that kidney transplantation from a donor with active BK viruria increased the recipient's risk of BK viremia.

The use of drugs for the induction and maintenance of immunosuppression is the most significant single factor in BKPyV reactivation. Induction therapy with antithymocyte globulins is associated with a longer duration of BKPyV viremia compared with anti-CD25 monoclonal antibodies or no induction therapy (71-73). Some studies have shown an association between tacrolimus and a higher frequency of BK viremia compared with cyclosporin (71). The use of the following combination: tacrolimus, mycophenolate, and corticosteroids, represents a high risk for BKPyV viremia compared with other therapy protocols (71). Also, the use of a urethral stent after transplantation is a constant risk factor for BK viremia (74). Male gender is a significant risk factor for BK viremia and the development of BKPyVAN, although the exact mechanism by which this occurs is still unknown (74-75).

Possibilities of laboratory diagnostics of BKPyV infection

Due to its significant clinical importance in the post-transplantation period, BKPyV is included in protocols for screening and monitoring kidney transplant patients. Because of the low specificity of BKPyV viruria and the high positive predictive value of BKPyV viremia, detection of BKPyV in blood (BK viremia) is the method of choice in these protocols (76). Regular screening of these patients, as well as timely preemptive reduction of immunosuppressive therapy in proven BKPyV viremia, can prevent the development of polyomavirus-associated nephropathy.

Nucleic acid amplification test (NAAT)

Detection of BKPyV DNA in urine

Detection of BKPyV DNA by PCR in urine is not recommended as a screening test due to low specificity. Also, all positive urine findings must be confirmed by a blood test, further increasing the cost of the diagnosis. Almost 50% of patients with BKPyV viruria will not develop BK viremia (77).

Detection of BKPyV DNA in blood

The recommended method for monitoring BKPyV in kidney transplant recipients is quantitative PCR to determine viremia (i.e., *viral load*) in the patient's blood. This test has a higher positive predictive value compared to the detection of BKPyV DNA in urine. Primers and probes that amplify highly conserved regions of the VP1, TAg, or NCRR genes are most commonly used for BKPyV detection and quantification. In addition to quantifying viral DNA, quantifying BKPyV mRNA allows detection of active viral transcription and infection (78). Also, this method is used to monitor the effectiveness of therapy for active BKPyV infection.

Genotyping of BKPyV

Sanger sequencing is still the most commonly used method for BKPyV genotyping. The relatively short BKPyV genome segment needs to be sequenced to determine BKPyV subtypes/subgroups. The obtained viral sequences are then compared to reference sequences for each subtype/subgroup, and based on single-nucleotide polymorphisms within the VP1 region, the final identification of BKPyV subtypes is performed. Having information on the distribution of BKPyV subtypes is crucial for improving diagnostic tests, designing studies on the immune response to infection caused by different BKPyV subtypes, and the potential development of vaccines against BKPyV infection (51).

BKPyV subtype I (Dunlop isolate) is used as a reference sequence for primer and probe design for diagnostic tests (79). BKPyV PCR assays, where primers and probes are defined according to subtype I as reference, can be four times (4x) less sensitive for the detection of other subtypes (79). This may lead to the failure to detect rare

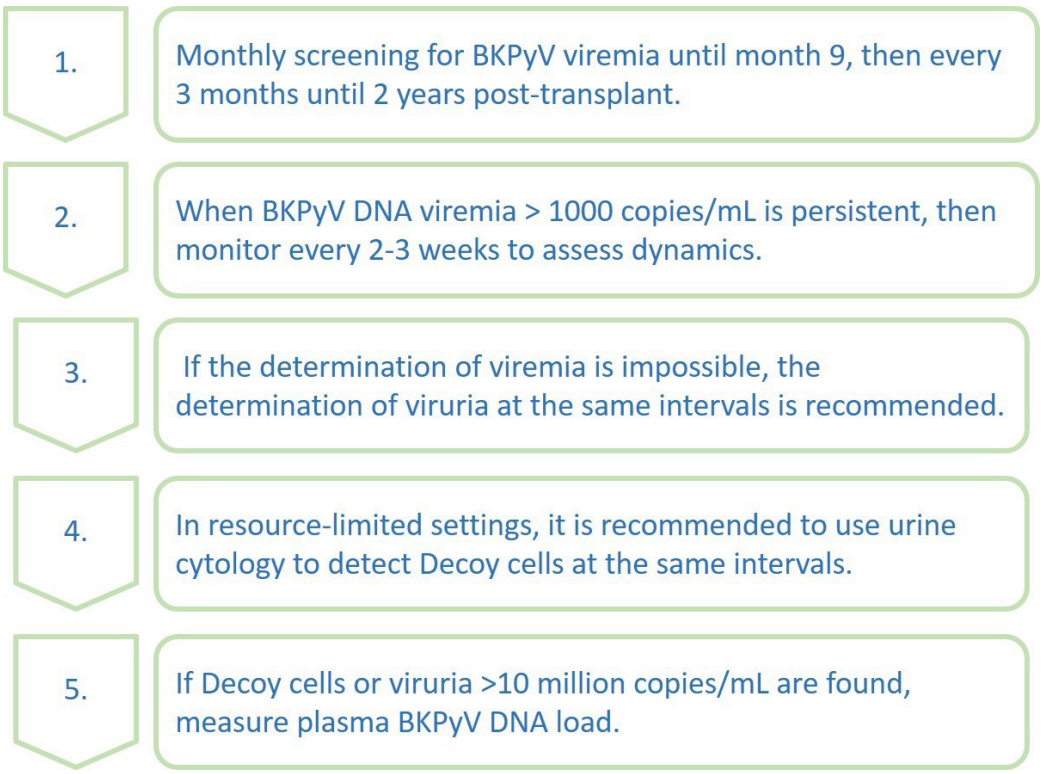

Figure 1. Recommendations for post-transplant testing for BKPyV in kidney recipients

subtypes (II and III) and, therefore, when there is polyomavirus-associated nephropathy with low BKPyV viremia, rarer BKPyV subtypes may be causative agents (4).

Urine cytology

BKPyV-infected cells on urine cytology are called *Decoy cells*. Decoy cells are tubular epithelial or uroepithelial cells with nuclear inclusions bordered by condensed chromatin (4). Decoy cells are a sign of polyomavirus replication but not an automatic diagnosis of polyomavirus-associated nephropathy (4). Also, other viruses, such as JCPyV and CMV, can lead to the formation of Decoy cells.

Biopsy of a transplanted kidney

Biopsy of the transplanted kidney remains the gold standard for diagnosing polyomavirus-associated nephropathy. Criteria for making a definitive diagnosis of BKPyV-associated nephropathy include characteristic cytological changes and positive immunohistochemistry with antibodies specific for polyomavirus.

Recommendations: diagnostics of BKPyV in kidney recipients' post-transplantation

According to "The second international consensus guidelines on the management of BK polyomavirus in kidney transplantation", the recommendations for post-transplant testing for BKPyV in kidney recipients presented in **Figure 1** (80).

Depending on the methodology used, the diagnosis of BKPyV-associated nephropathy can be (80):

1. **Possible BKPyV nephropathy** - BKPyV viruria >10 million copies/ml or Decoy cells or virions by electron microscopy without detectable BKPyV viremia.
2. **Probable BKPyV nephropathy** - BKPyV DNA viremia >1000 copies/mL sustained > 2 weeks.
3. **Presumed BKPyV nephropathy** - BKPyV DNA viremia >10,000 copies/mL.
4. **Biopsy-proven BKPyV nephropathy** - detection of specific cytological changes + immunohistochemistry and specific tests to identify BKPyV and distinguish it from JCPyV.

CONCLUSION

As a consequence of using potent immunosuppressants after transplantation, BKPyV infection is a risk factor for graft loss following kidney transplantation. Since there is no specific antiviral treatment for BKPyV, regular monitoring of kidney transplant recipients remains crucial in modern transplant medicine. Additionally, further research into specific treatments for BKPyV is necessary to establish the most effective therapeutic protocols for managing BKPyV infection post-transplant.

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INFEKCIJA BK POLIOMAVIRUSOM (BKPYV) KOD TRANSPLANTACIJE BUBREGA: KARAKTERISTIKE VIRUSA, GENETSKA RAZNOVRSNOST, REAKTIVACIJA, FAKTORI RIZIKA I LABORATORIJSKA DIJAGNOSTIKA

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Sažetak

BK poliomavirus (BKPyV) je široko rasprostranjeni humani poliomavirus. Nakon primarne infekcije, koja je obično asimptomatska, BKPyV uspostavlja doživotnu perzistenciju u ćelijama bubrežnog epitela. Poslednjih godina, zbog upotrebe snažnih imunosupresivnih lekova nakon transplantacije došlo je do povećanja učestalosti reaktivacije BKPyV kod pacijenata sa transplantiranim organima, izdvajajući BKPyV kao jedan od glavnih faktora rizika za gubitak kalema kod primalaca transplantiranog bubrega. Ovaj pregledni rad pisan iz perspektive virusologa daje detaljan uvid u BKPyV infekciju sa posebnim osvrtom na reaktivaciju posle transplantacije bubrega. Prvi deo rada pruža uvid u strukturu viriona, organizaciju genoma, životni ciklus, mehanizme doživotne perzistencije kao i osnovne epidemiološke podatke u vezi sa BKPyV infekcjom. Mesto preplitanja osnovne i kliničke virusologije objašnjeno je kroz diverzitet BKPyV kao i klinički značaj istog. Dalje se u radu obrađuju klinički aspekti BKPyV infeckije, uključujući faktore rizika za reaktivaciju BKPyV, klinički značaj tipizacije izolata kao i značaj serotip-specifičnog imuniteta. U drugom delu rada, naglasak je na mogućnostima laboratorijske dijagnostike BKPyV infekcije. Na kraju se nalaze aktuelne međunarodne preporuke za skrining i praćenje BKPyV infekcije u posttransplantacionom periodu. Ovaj pregledni rad kombinovanjem virusoloških, kliničkih i dijagnostičkih aspekata ističe složenost BKPyV infekcije nakon transplantacije bubrega. Takođe, ukazuje na potrebu za daljom optimizacijom monitoringa BKPyV infekcije, dodatnim istraživanjima kliničkog značaja virusnog diverziteta kao i unapređenje terapijskih protokola za kontrolu BKPyV infekcije nakon transplantacije bubrega.

Ključne reči: BK poliomavirus, BKPyV, poliomavirus udružena nefropatija, faktori rizika, transplantacija bubrega

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