Polyomavirus in Organ Transplants
New Updates in Diagnosis, especially in pathology and Management

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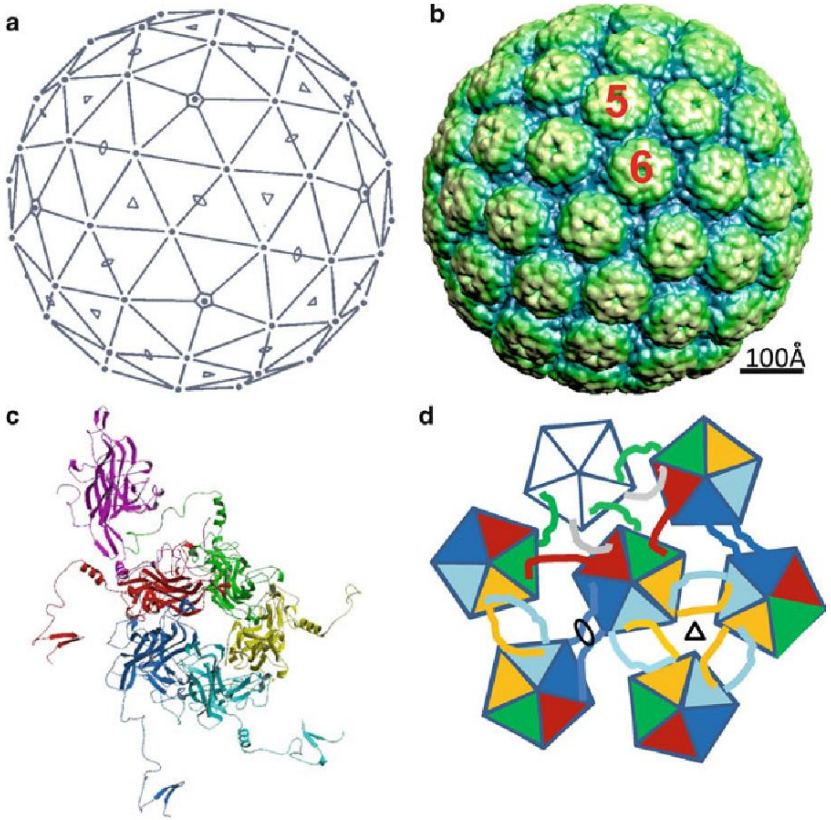
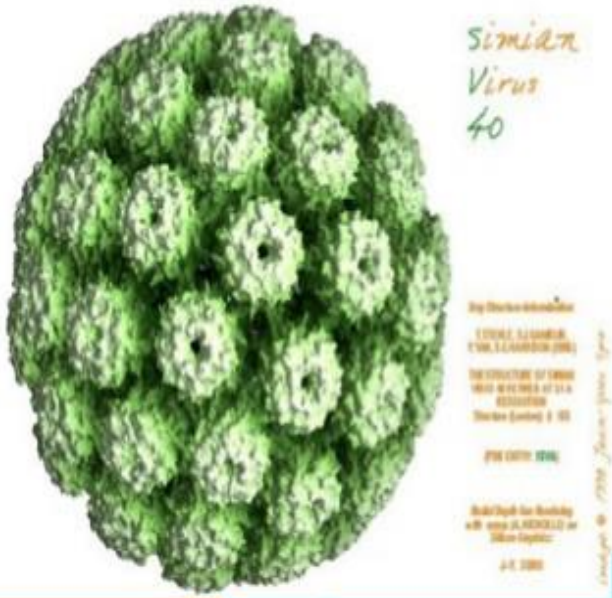
- 25 Feb 21

A 62 yo male with ph of DM and HTN after 2 month of HD underwent kidney transplantation. He received kidney from a deceased donor, 50 yo male. Both recipient and donor have iso BG. PRA test was 5%. Recipient received MP 500 mg, and Anti-thymocyte globulin for 4 following days of transplantation. He received Tacrolimus, Mycophenolate mofetil, and prednisone as immunosuppressive drugs. Plasma creatinine at discharge date was 1.5 mg/dL. Three month later he admitted to hospital because of silent rise in plasma creatinine of 2.5mg/dL. Physical exam was unremarkable. Ultrasonography was normal. Tacrolimus blood level was in the range. Urinary sediment was normal. CMV was –ve. Decoy cell was seen in urine. Attending physician request for BK virus in blood and urine. Virus copy in blood was 150,000, and in urine was 350,000. Interstitial nephritis was seen in kidney biopsy. Tacrolimus switched to Rapamune and mycophenolate mofetil was discontinued. The patient received IVIG for one week. After 3 month plasma creatinine was 1.2mg/dL, and blood viremia was cleared.

Polyomaviruses Family



POLYOMAVIRUSES



These include SV40, BK, JC and polyoma viruses.

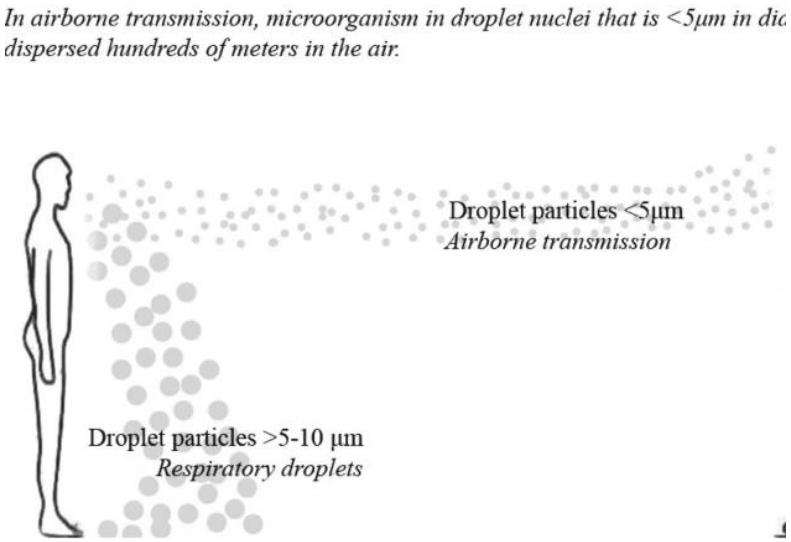
All have a similar strategy for DNA replication.

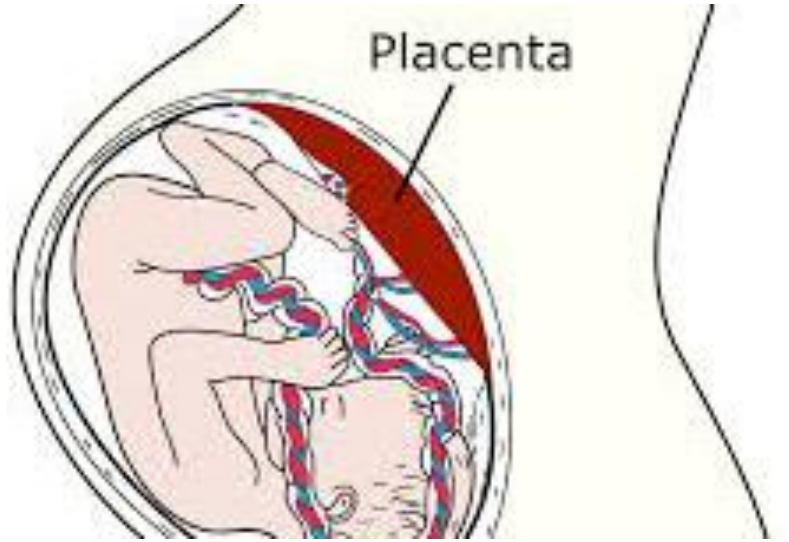
They are small (~40nm diameter), icosahedral, non-enveloped viruses that replicate in the nucleus. Depending on the host cell, they can either transform the cell or replicate the virus and lyze the cell.

SV40 virus, a polyoma virus

BK Polyomavirus Virus Glomerular Tropism:Implications for Virus Reactivation from Latency and Amplification during Immunosuppression. Donald J. Alcendor
J. Clin. Med. 2019, 8, 1477

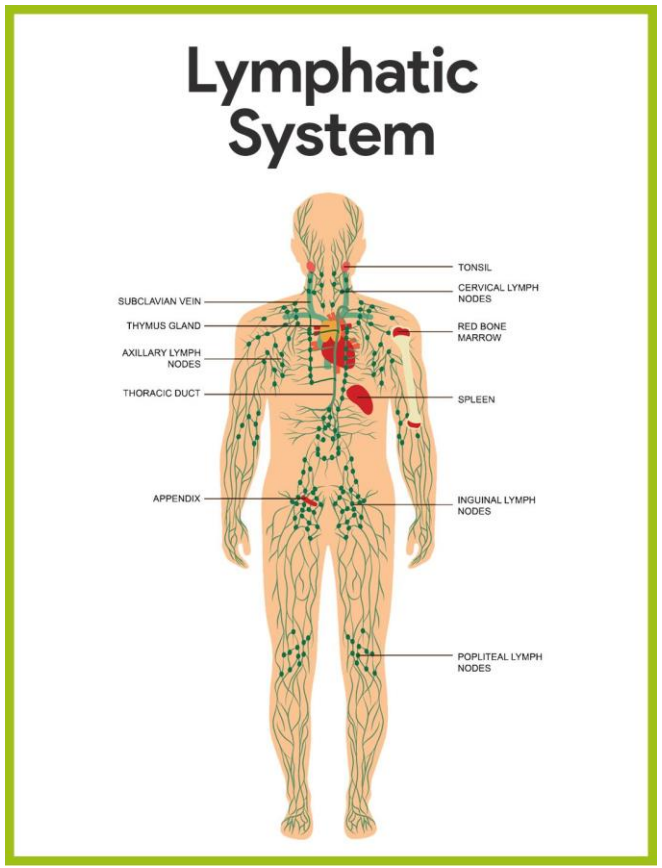
Route of transmission

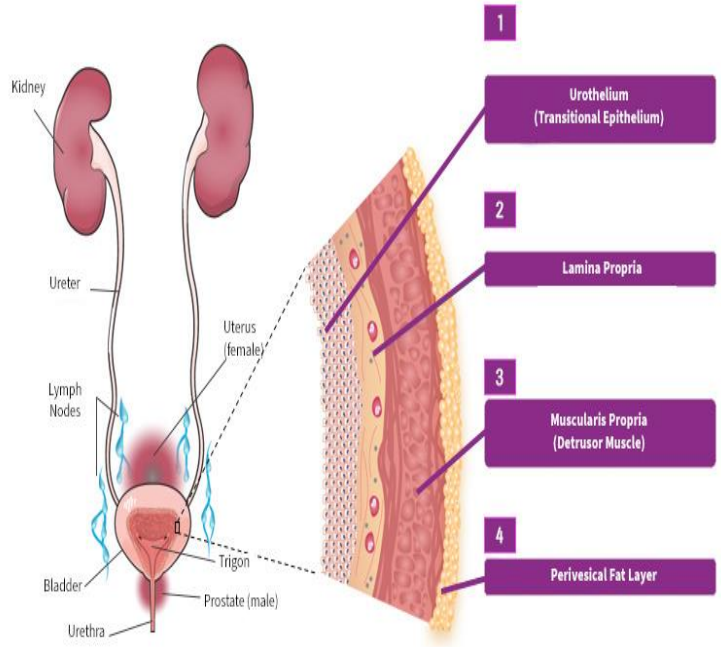




Bohl DL, Brennan DC. BK virus nephropathy and kidney transplantation. Clinical Journal of the American Society of Nephrology. 2007;2(Supplement 1):S36-S46

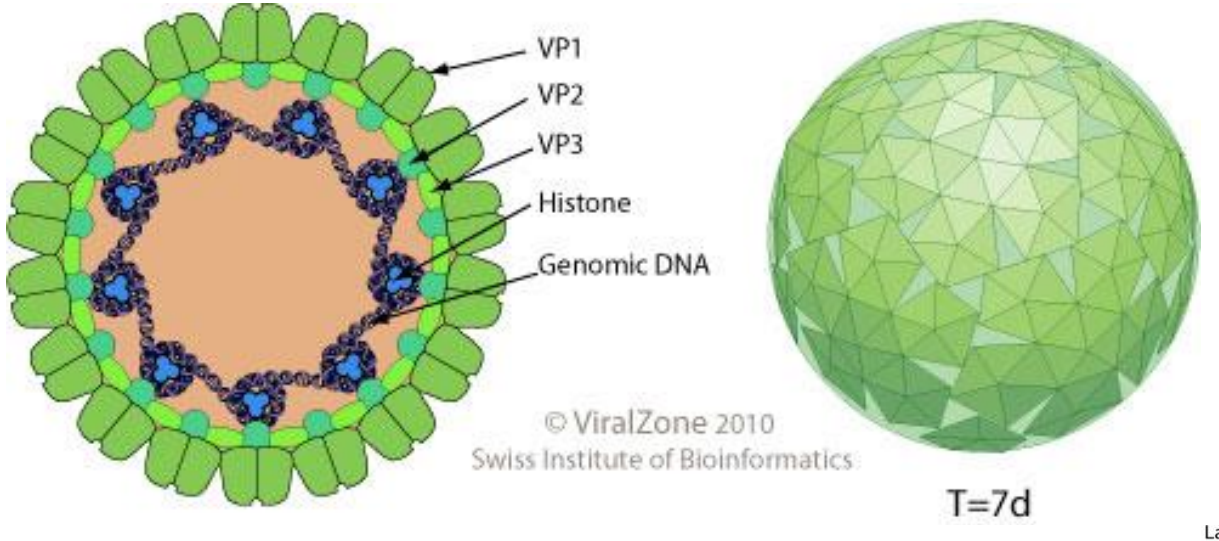
After primary infection, the virus located in the following places and then enter the latent phase.

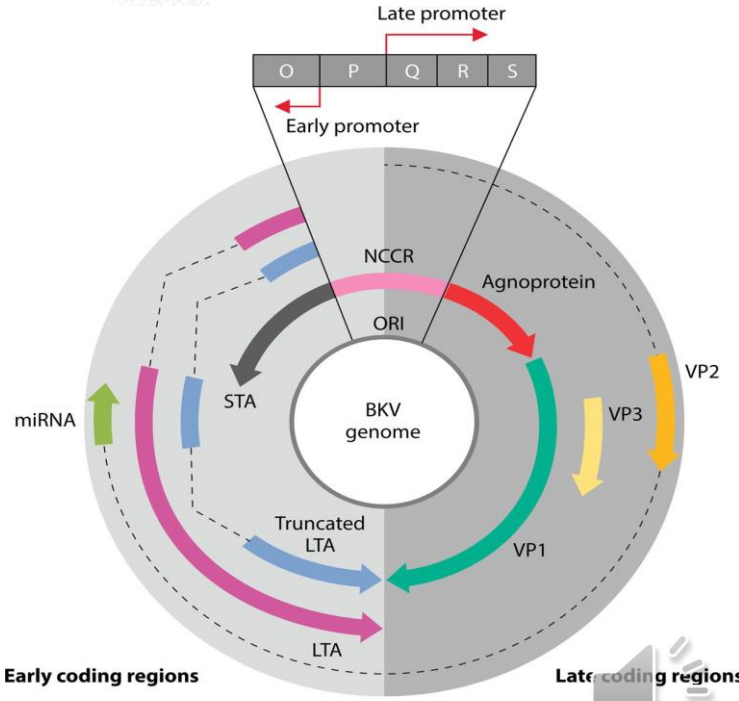




Bohl DL, Brennan DC. BK virus nephropathy and kidney transplantation. Clinical Journal of the American Society of Nephrology. 2007;2(Supplement 1):S36-S46

The BK virus was first isolated from the urine of a renal transplant recipient with ureteric stenosis in 1971, but it was not until 20 years later that BK was recognized as a cause of interstitial nephritis and allograft failure in renal transplant recipient.



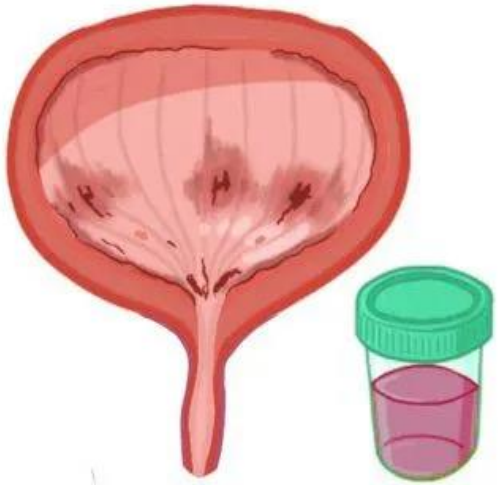


- BK virus infection: an update on diagnosis and treatment
- Deirdre Sawinski and Simin Goral
- Nephrol Dial Transplant (2015) 30: 209–217 doi: 10.1093/ndt/gfu023

- Factors and outcome in BK virus nephropathy in a Hispanic kidney transplant population D. Pe´rez-Torres, J. Bertra´n-Pasarell,E, et al.
- Transplant Infectious Disease 2010: 12: 16-22

BK VIRUS (BKV)

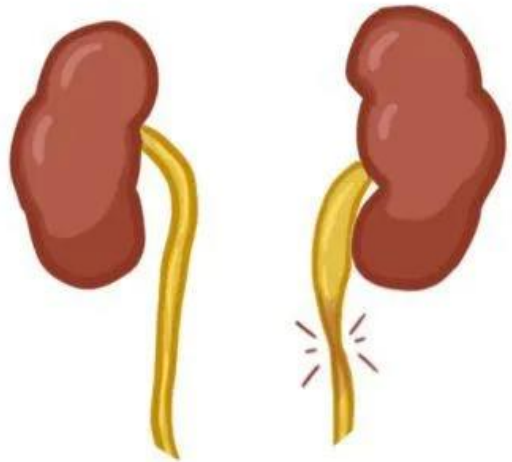
CLINICAL MANIFESTATIONS



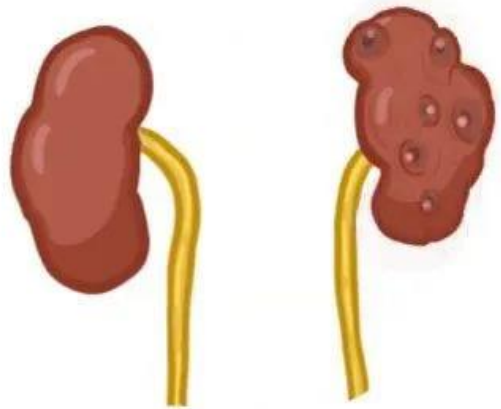
HEMORRHAGIC CYSTITIS

↳ BLOODY URINE

↳ BONE MARROW TRANSPLANT RECIPIENTS

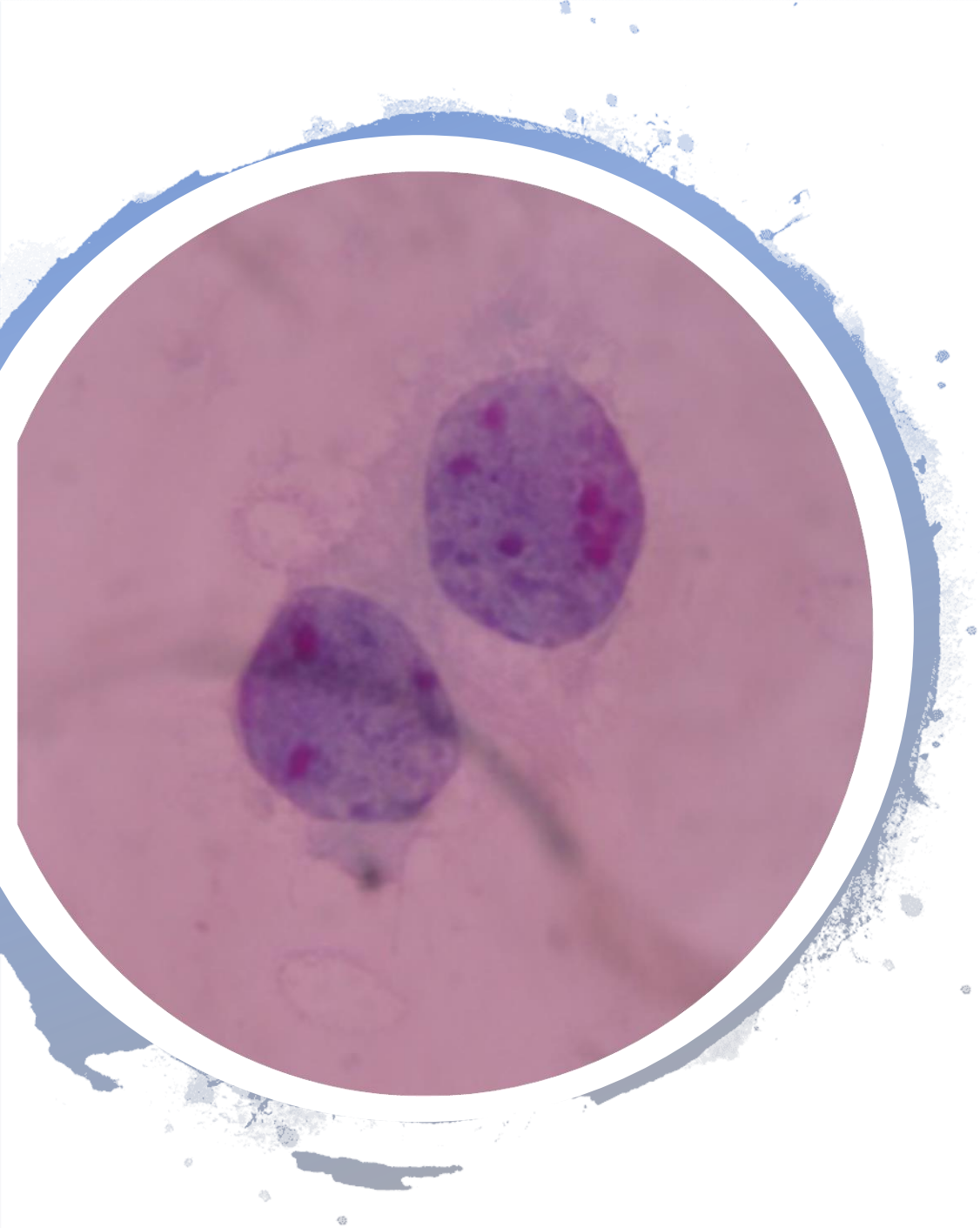


URETERAL STENOSIS



NEPHROPATHY

↳ KIDNEY TRANSPLANT P



- Management of BKPolyomavirus Infection inKidney and Kidney-PancreasTransplant Recipients A Review Article Nissreen Elfadawy, MS, MDa, Masaaki Yamada, MD, Nagaraju Sarabu, MD Infect Dis Clin N Am 32 (2018) 599–613

- Influence of surveillance renal allograft biopsy on diagnosisand prognosis of polyomavirus-associated nephropathyCHRISTOPHER K. BUEHRIG, DONNA J. LAGER, MARK D. STEGALL, MICHELLE A. KREPS,WALTER K. KREMERS, JAMES M. GLOOR, THOMAS R. SCHWAB, et al. Kidney International, Vol. 64 (2003), pp. 665–673

BKV is ubiquitous, with a worldwide seroprevalence in adults of 75% (range 46%–94%).

Primary infection with BKV (flu-like syndrome) typically occurs in early childhood with an adult seroprevalence rate of 80%.

The virus remains latent in urothelium and reactivation (asymptomatic) is often the result of immunosuppression.

Following renal transplantation, asymptomatic shedding of virally loaded urothelial “decoy” cells can be detected in the urine in 10% to 30% of recipients.

BKV and JCV are 70% related in their genome sequence.

This similarity between the genomes of BK & SV40 enables SV40 to be a marker for immunohistochemical staining, which is vital in diagnosis of BKVAN.

Based on DNA sequence variations, BK can be divided into six subtypes or genotypes. Genotype I is the most frequent worldwide (80%), followed bygenotype IV (15%).

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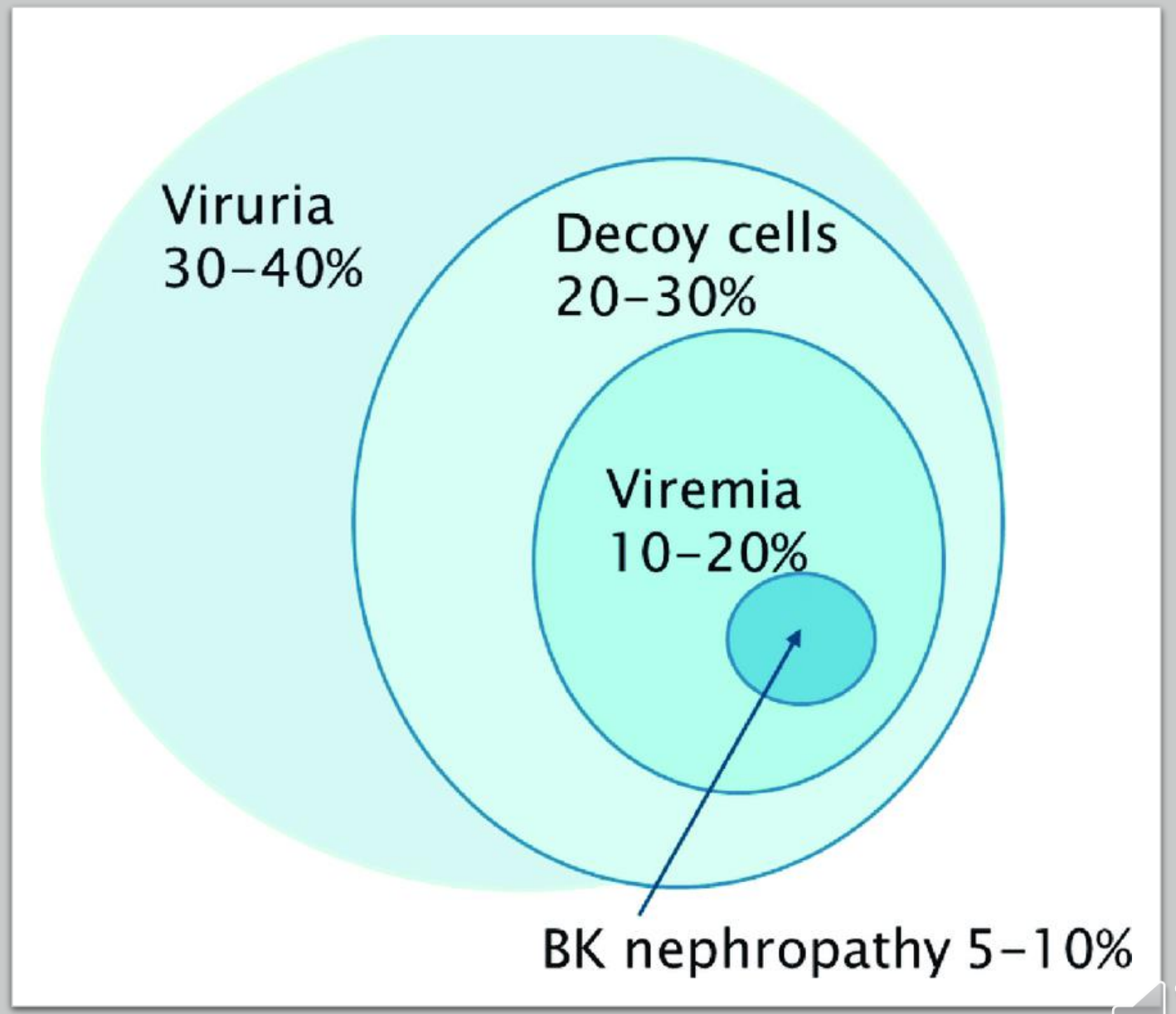
- Polyoma virus nephropathy in kidney transplantation Jacob RW Scadden, Adnan Sharif, Kassi Skordilis, Richard Borrows
- World J Transplant 2017 December 24; 7(6): 329-338.

- BK virus infection: an update on diagnosis and treatment Deirdre Sawinski and Simin Goral
- Nephrol Dial Transplant (2015) 30: 209–217 doi: 10.1093/ndt/gfu023

- BK Virus Nephropathy and Kidney Transplantation. Daniel L. Bohl and Daniel C. Brennan. Clin J Am Soc Nephrol 2: S36–S46, 2007. doi: 10.2215/CJN.00920207

Type and prevalence of BKV infections in KTRs.

Rare cases of nephropathy without viremia or viremia without viruria may occur



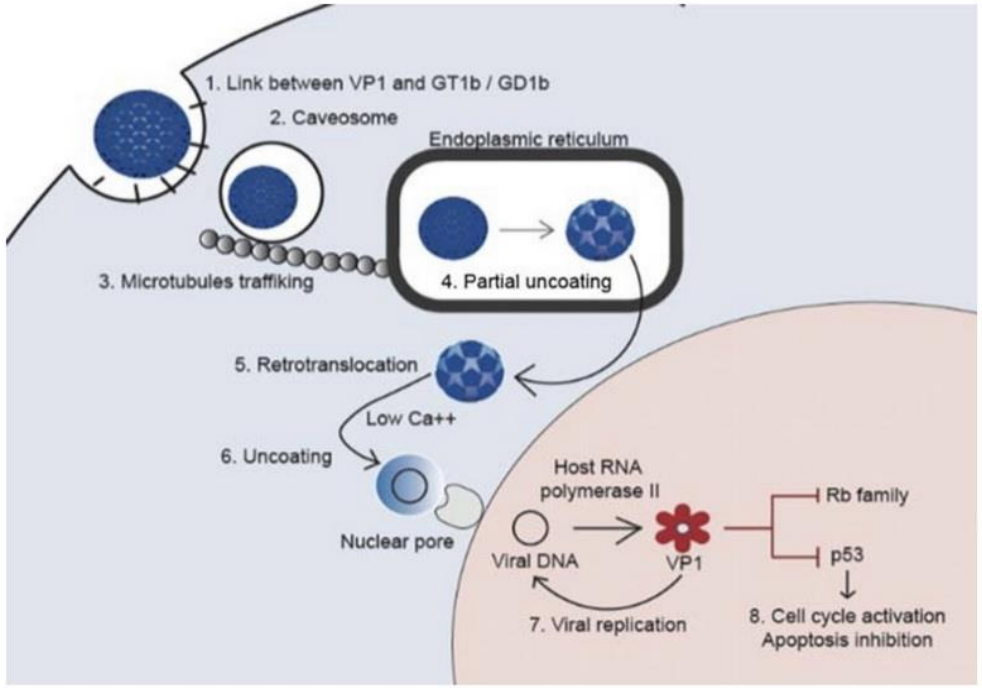


FIGURE 1. BK polyomavirus cell entry and infection. Representation of mechanisms of viral cell entry, trafficking, and infection highlighting action on the cell cycle machinery.

- Lamarche C, Orio J, Collette S, Senécal L, Hébert M-J, Renoult É, et al. BK polyomavirus and the transplanted kidney: immunopathology and therapeutic approaches. Transplantation. 2016;100(11):2276

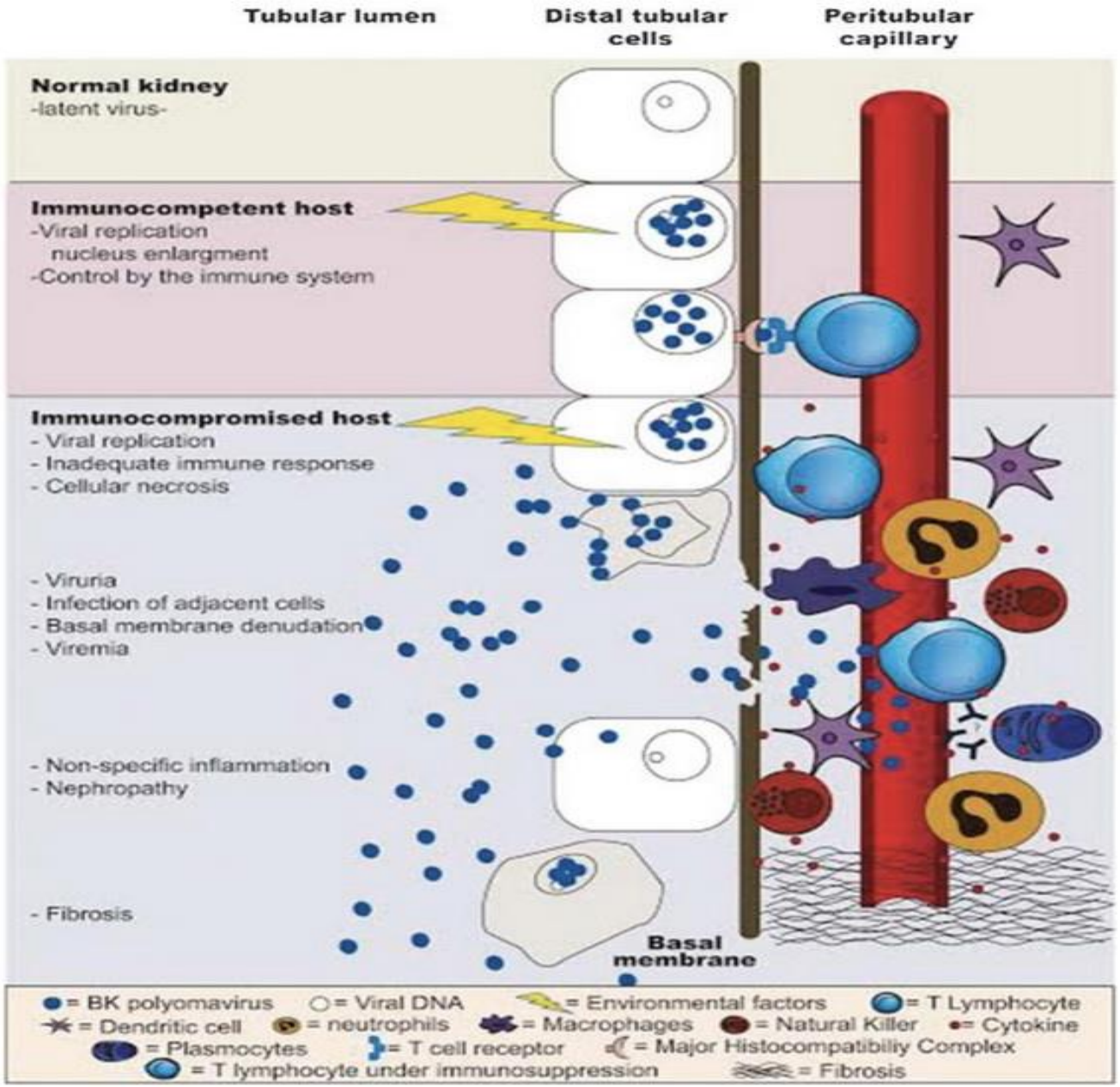


FIGURE 2. Physiopathology of PVAN. Depiction of PVAN development form latency in the uroepithelium (top) to the development of renal inflammation and fibrosis (bottom).

Lamarche C, Orio J, Collette S, Senécal L, Hébert M-J, Renoult É, et al. BK polyomavirus and the transplanted kidney: immunopathology and therapeutic approaches. Transplantation. 2016;100(11):2276

Elfadawy et al

Table 1
Risk factors of BK virus reactivation and BK virus–associated nephropathy

Risk Factors of BKV Reactivation After Transplantation

Recipient-Related	Donor-Related	Transplant-Related
• Older age • Male gender • Steroid exposure • Antirejection treatment • Diabetes mellitus • Negative BKV serostatus	• Female gender • African American • Deceased donors • BKV seropositive status	• High immunosuppression drug levels • Use of tacrolimus • Thymoglobulin induction • Ureteral stents • HLA mismatch • A,B, OR O blood groups incompatibility • Ischemia or reperfusion injury • Long ischemia time

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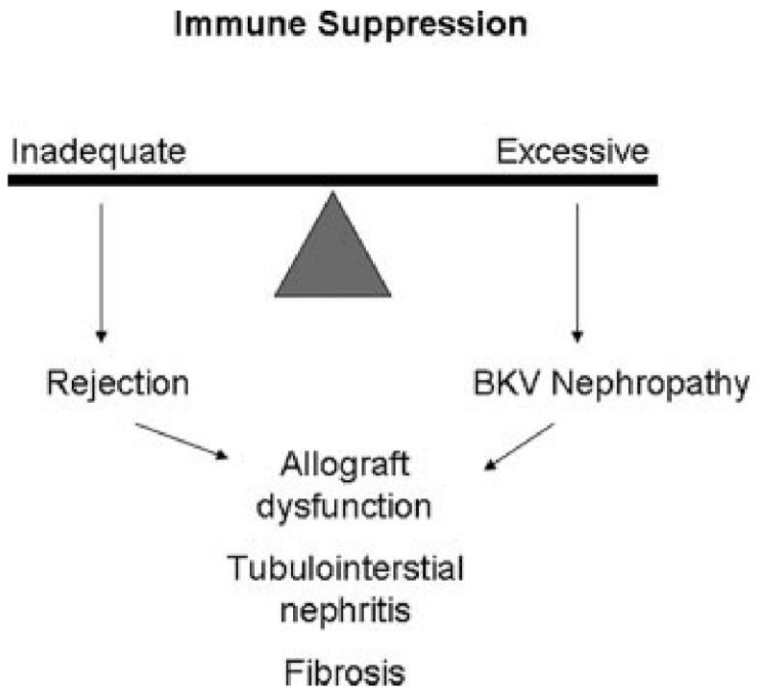


Figure 3. Impaired immune suppression balance. Inadequate immune suppression results in rejection, whereas excessive immune suppression results in BKV nephropathy. Both conditions present as allograft dysfunction with tubulointerstitial nephritis and progression to fibrosis.

- BK Virus Nephropathy and Kidney Transplantation. Daniel L. Bohl and Daniel C. Brennan. Clin J Am Soc Nephrol 2: S36–S46, 2007. doi: 10.2215/CJN.00920207

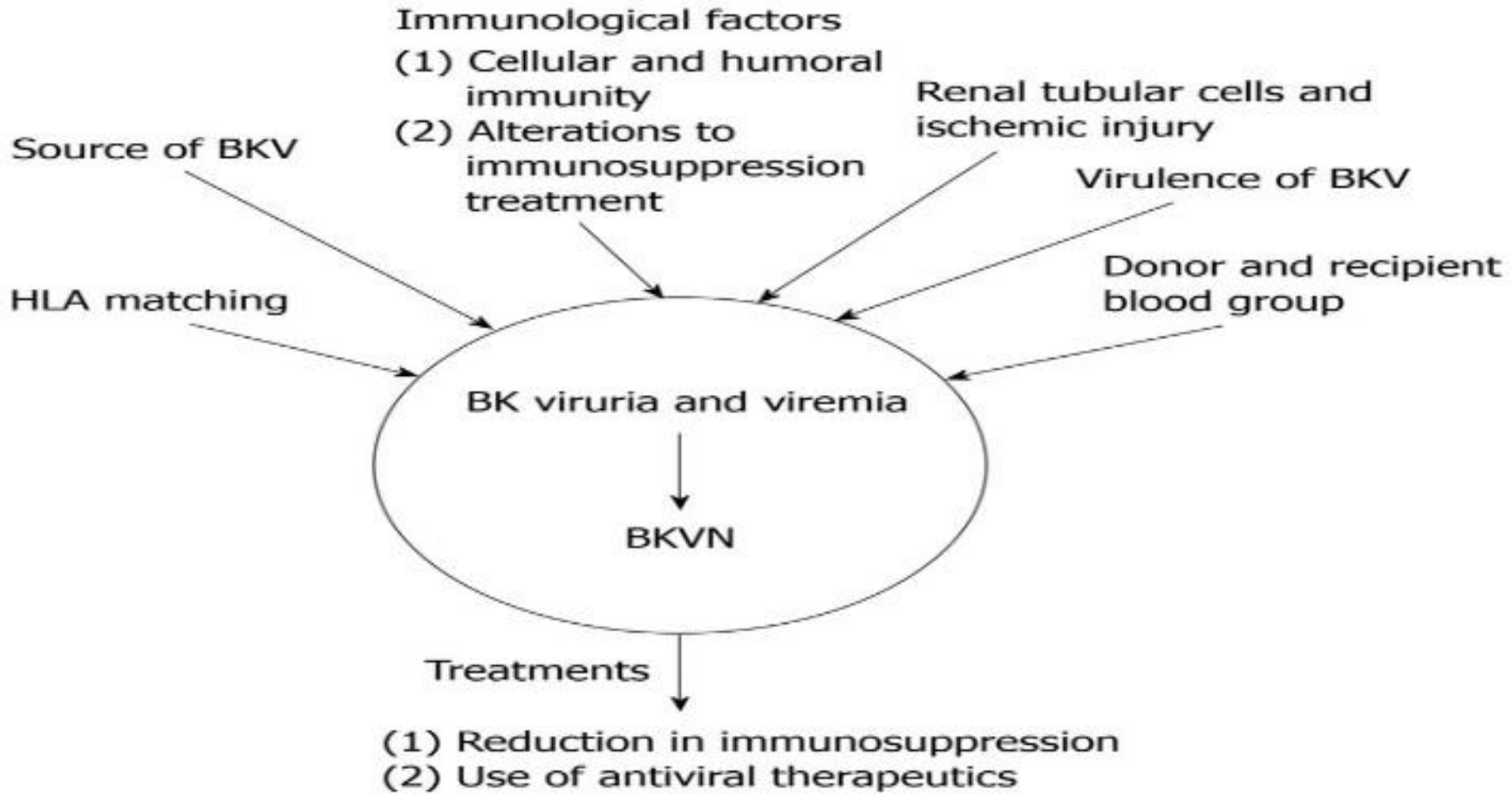


Figure 1 Proposed mechanisms for the pathogenesis of BK virus-associated nephritis after BK virus infection has occurred resulting in BK viruria or BK viremia. These mechanisms include immunological factors, such as alterations to immunosuppressive therapy and cellular and humoral immunity, the source of BKV, either from the recipient or the donor, HLA matching, donor and recipient blood group. The two main treatment options for BKVN are a reduction in immunosuppression and the use of antiviral therapies. These treatments can also be used for BK viruria and viremia in order to prevent progression to BKVAN. BKV: BK virus; BKVAN: BK virus-associated nephritis.

Scadden JR, Sharif A, Skordilis K, Borrows R. Polyoma virus nephropathy in kidney transplantation. World journal of transplantation. 2017;7(6):329

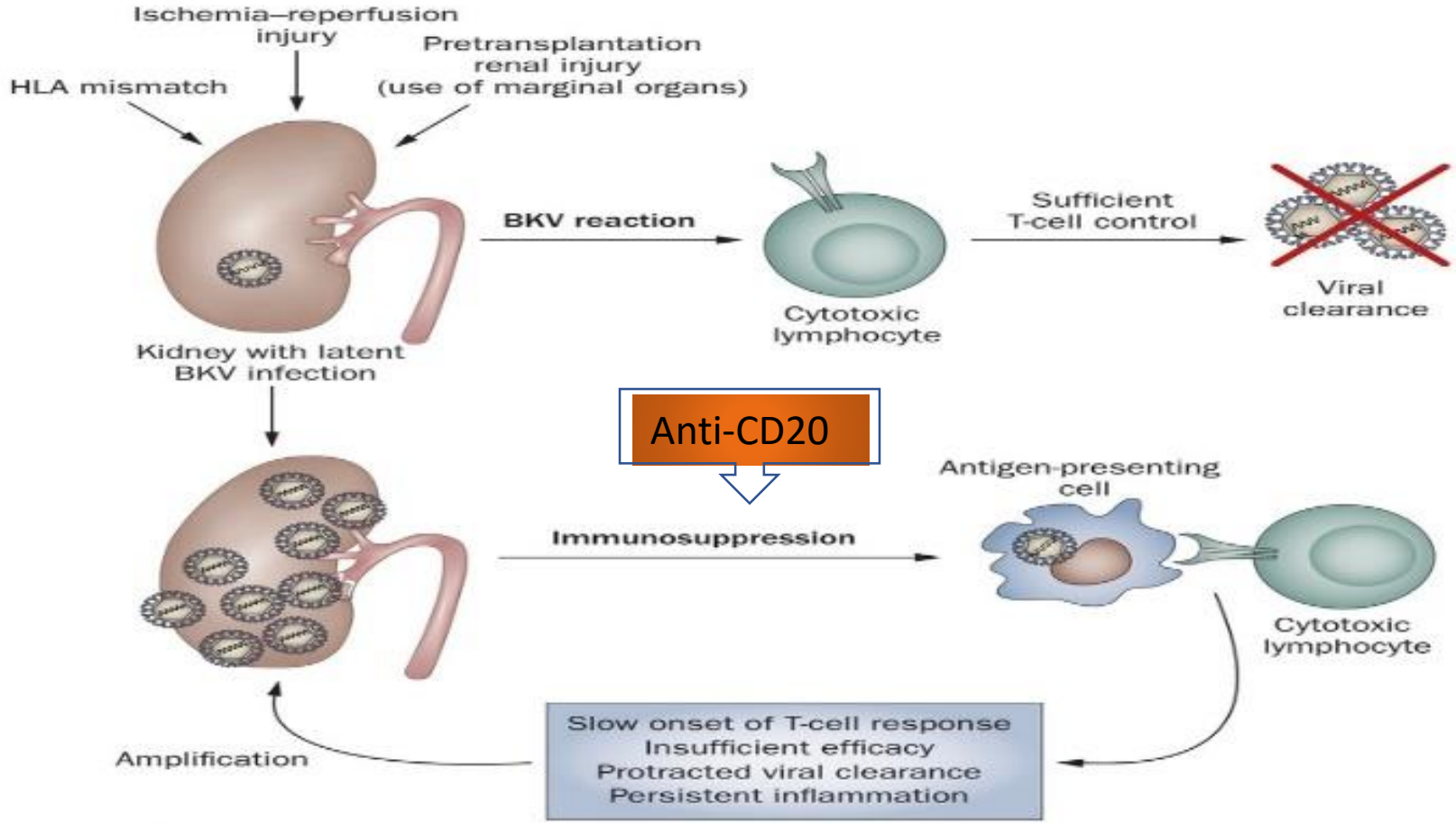


Figure 1 | The functional activity of BKV-specific T cells seems to determine the clinical outcome of BKV reactivation. A sufficient BKV-specific T-cell response is able to control BKV replication and prevent progression of BKV infection to BKVAN. By contrast, insufficient or only partial T-cell-mediated responses to BKV lead to protracted virus elimination and persistent intragraft inflammation. As a consequence, activated BKV-specific or alloantigen-specific cytotoxic T cells migrate into the inflamed area and attack graft cells that express either BKV peptides or donor MHC antigens. This tissue damage further increases intragraft inflammation, which can accelerate BKV proliferation (as is known to occur for other viruses), cause homing of more activated cytotoxic T cells, and ultimately lead to BKVAN. Abbreviations: BKV, BK virus; BKVAN, BK-virus-associated nephropathy.

Babel N, Volk H-D, Reinke P. BK polyomavirus infection and nephropathy: the virus–immune system interplay. Nature Reviews Nephrology. 2011;7(7):399

BK reactivation and urinary shedding of BK virus have been reported in otherwise healthy, immunocompetent patients, but it is uncommon.

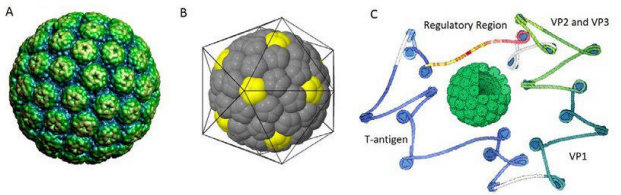
Outside of renal transplantation, BK is mostly encountered in bone marrow transplant recipients; in these patients, BK infection can present either as BKVN or hemorrhagic cystitis.

There have been scattered case series reporting detectable BKV and BK viruria in nonrenal solid organ transplant recipients (heart, lung and liver), but in general the presence of BK in blood or urine has not been associated with impaired renal function in these patients.

- BK virus infection: an update on diagnosis and treatment Deirdre Sawinski and Simin Goral. Nephrol Dial Transplant (2015) 30: 209–217 doi: 10.1093/ndt/gfu023

SV40

a simian virus,was introduced into the human population through contaminated polio and adenovirus vaccines.



It can be acquired through close contact with nonhuman primates and may spread at a low rate from person to person.

Although SV40 has been identified in kidney transplant biopsies and associated with native kidney diseases, its importance in kidney transplantation is poorly defined.

Bohl DL, Brennan DC. BK virus nephropathy and kidney transplantation. Clinical Journal of the American Society of Nephrology. 2007;2(Supplement 1):S36-S46

JCV is the causative agent for the neurological disease progressive multifocal leukoencephalopathy(PML), which occurs primarily in AIDS patients.

JCV has been identified in kidney biopsy tissue and urine by immunohistochemistry and PCR, respectively, from a subset of RTPs with tubulointerstitial nephritis.
However, its role as a cause of PVAN remains to be defined.

Saundh BK, Tibble S, Baker R, Sasnauskas K, Harris M, Hale A. Different patterns of BK and JC polyomavirus reactivation following renal transplantation. Journal of clinical pathology. 2010;63(8):714-8

JCV PML

Progressive multifocal leukoencephalopathy and other forms of JC virus disease
Bruce J. Brew, Nicholas W. S., Ext al. Brew, B. J. et al. Nat. Rev. Neurol. 6, 667–679 (2010); doi:10.1038/nrneurol.2010.164

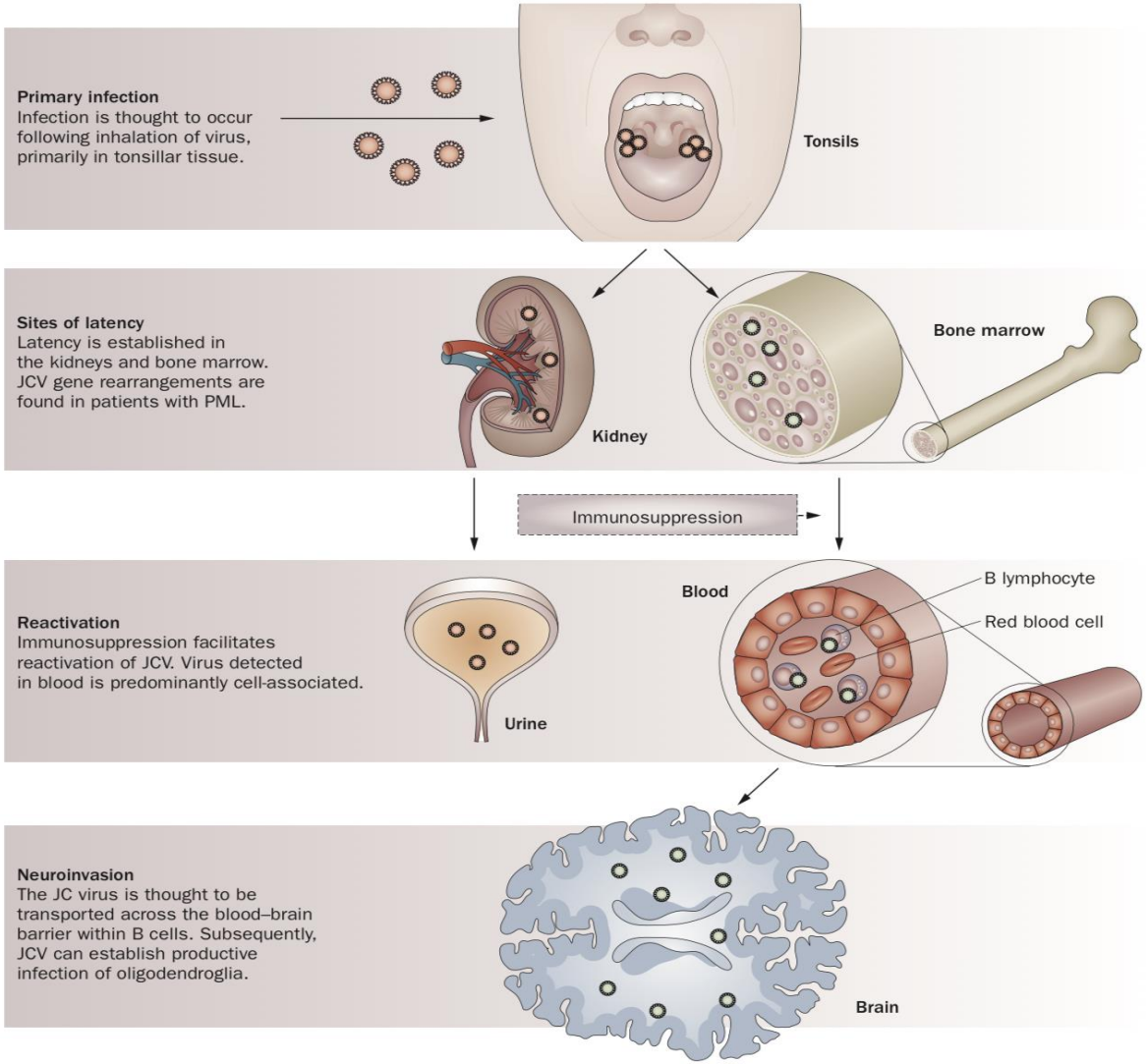


Figure 1 | Proposed disease course of PML. Initial JCV infection is thought to occur in tonsillar tissue after inhalation. Lymphocytes infected with JCV carry virions to the kidney and bone marrow, which are thought to be the primary sites of viral latency. Following reactivation of JCV, the virus is thought to cross the blood–brain barrier within B cells and infect oligodendroglia. The change in JCV color from red to green indicates genetic rearrangement. Abbreviations: JCV, JC virus; PML, progressive multifocal leukoencephalopathy.

JCV
PML

Progressive multifocal leukoencephalopathy and other forms of JC virus disease
Bruce J. Brew, Nicholas W. S., Ext al. Brew, B. J. et al. Nat. Rev. Neurol. 6, 667–679 (2010); doi:10.1038/nrneurol.2010.164

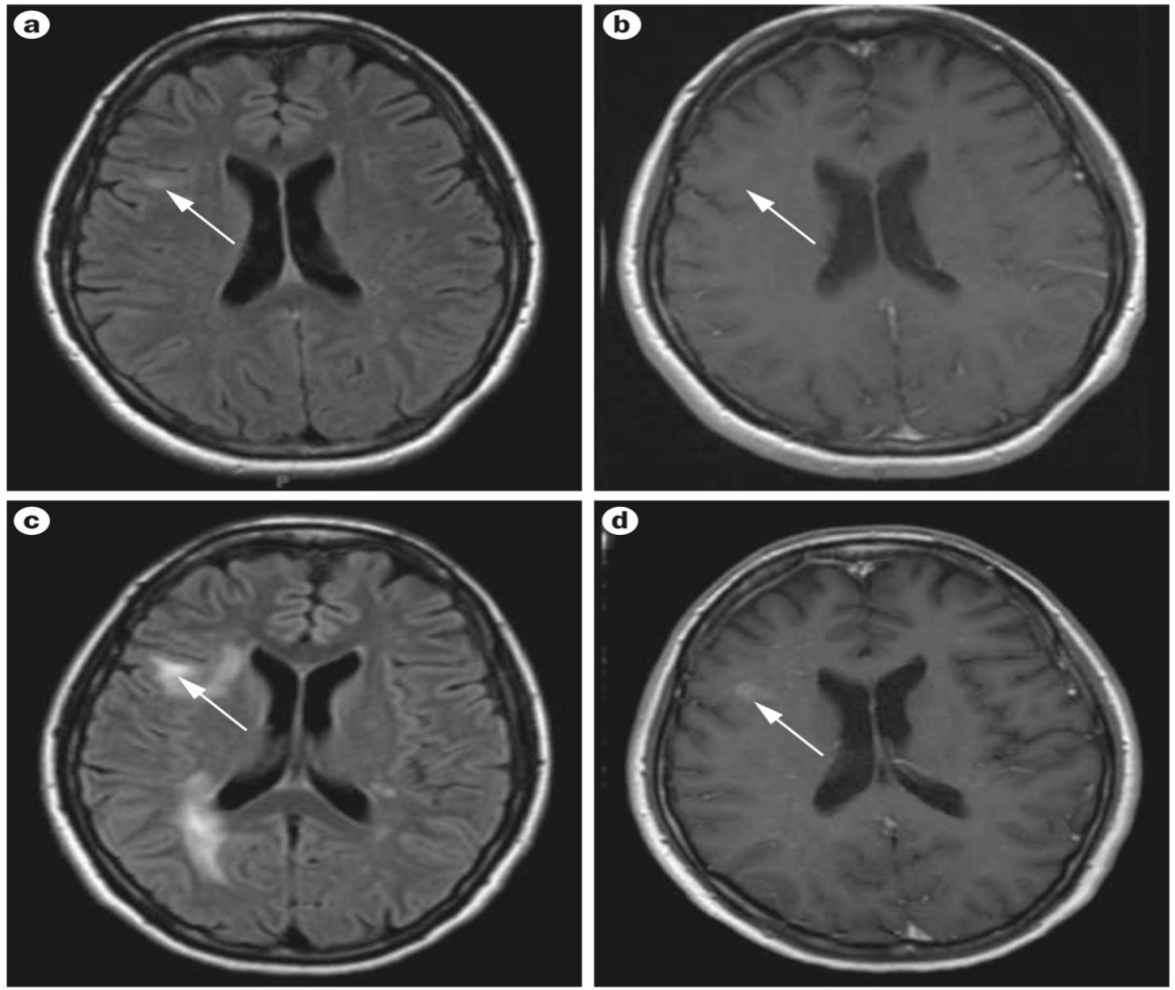


Figure 2 | FLAIR images showing progression of progressive multifocal leukoencephalopathy immune reconstitution inflammatory syndrome. **a** | Multifocal, high-signal-intensity lesions (arrow) in the right hemisphere of a patient after prolonged immunosuppressive therapy for a lung transplant. The cerebrospinal fluid was positive for JC virus. **b** | Contrast enhancement is not evident (arrow) in immune reconstitution inflammatory syndrome lesions. **c** | 6 weeks later, progression of the white matter lesions (arrow) shows involvement of the uncinate fibers. **d** | Patchy enhancement with gadolinium (arrow) is noted (predominantly in the right hemisphere), which is indicative of immune reconstitution inflammatory syndrome. Abbreviation: FLAIR, fluid-attenuated inversion recovery.

Polyomavirus Complications

1- Tubulointerstitial nephritis, and if it is severe may lead to allograft failure.

2- BKV infection may prompt rejection, and the damage caused by rejection or its treatment may promote viral replication.

3- BKV can lead to production of DSAs which can cause ABMR.

4- BKV may cause uroepithelial cancer. In animals BKV frequently develops ependymomas, pancreatic islet tumors, osteosarcomas, fibrosarcomas, liposarcomas, osteosarcomas, nephroblastomas and gliomas.

5- JCV may lead to PML, and JCV DNA has been detected in various neoplastic lesions such as oligodendroglioma, astrocytoma medulloblastoma, ependymoma, glioblastoma, colorectal carcinoma, gastrointestinal and bladder cancers.

Pérez-Torres D, Bertrán-Pasarell J, Santiago-Delpín E, González-Ramos M, Medina-Mangual S, Morales-Otero L, et al. Factors and outcome in BK virus nephropathy in a Hispanic kidney transplant population. Transplant Infectious Disease. 2010;12(1):16-22

Sharma R, Zachariah M. BK Virus Nephropathy: Prevalence, Impact and Management Strategies. International Journal of Nephrology and Renovascular Disease. 2020;13:187

Gupta G, Kuppachi S, Kalil RS, Buck CB, Lynch CF, Engels EA. Treatment for presumed BK polyomavirus nephropathy and risk of urinary tract cancers among kidney transplant recipients in the United States. American Journal of Transplantation. 2018;18(1):245-52

Karimi Dehcheshmeh L, Makvandi M, Timori A. Prevalence of Human Polyomavirus JC and BK in Normal Population. Asian Pacific Journal of Cancer Prevention. 2020;21(10):2877-82

They are everywhere, take care.