The 19th International Congress of Nephrology, Dialysis and Transplantation (ICNDT)

12-15 December 2023
Homa Hotel, Tehran

Viral Infections in Renal TX Recipients: BK Virus

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21-24, 09 02

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BKV, a silent terminator

After 2 years of a successful kidney TX, her nephrologist noticed a gradual increase in creatinine from 1.3 to 2.5.

Lab findings for CMV and other routine lab including US was –ve.

Decoy cell was found in urine, subsequently BK viral load in serum and urine was 25000 and 15000 copies respectively.

Kidney BX showed interstitial nephritis, C4D –ve, compatible with BKV nephropathy.

Switching from tacrolimus to sirolimus resulted in disappearing BKV and returning of creatinine to baseline level 1.3.

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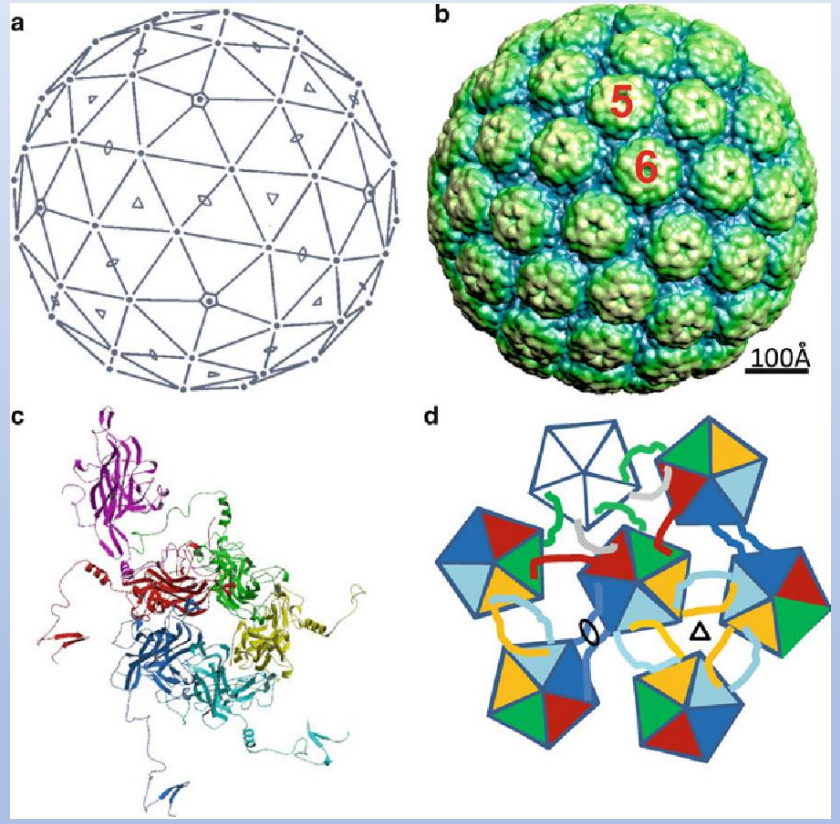
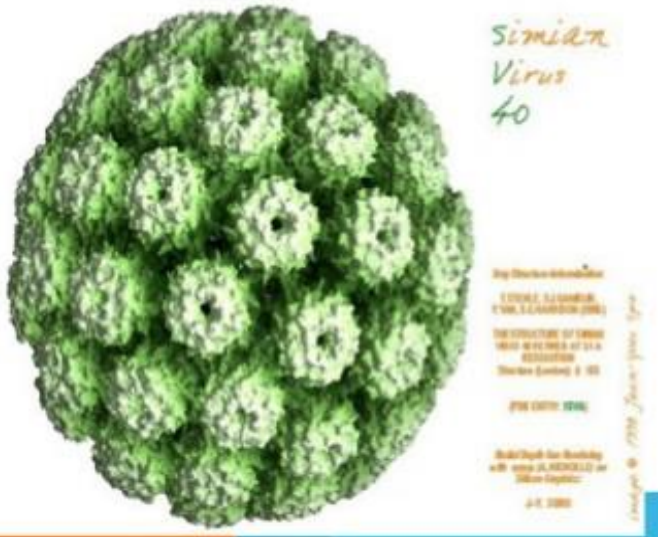
Polyomaviruses Family

✓



POLYOMAVIRUSES



These include SV40, BK, JC and polyoma viruses.

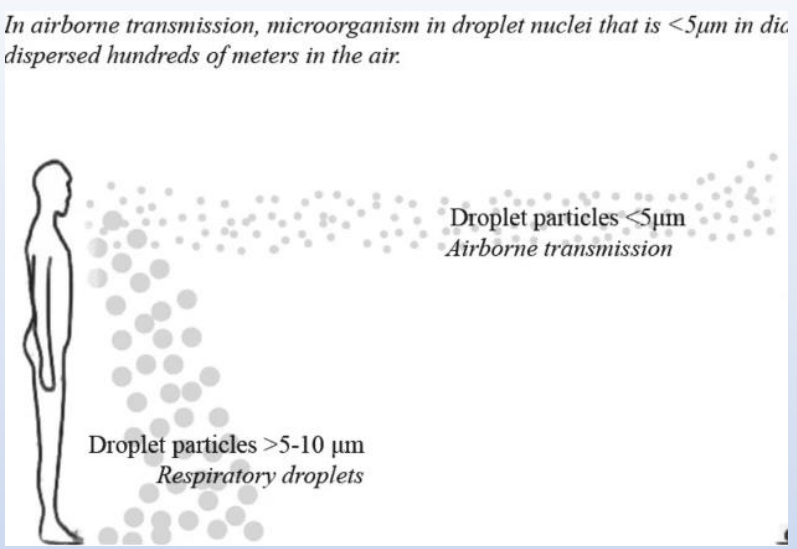
All have a similar strategy for DNA replication.

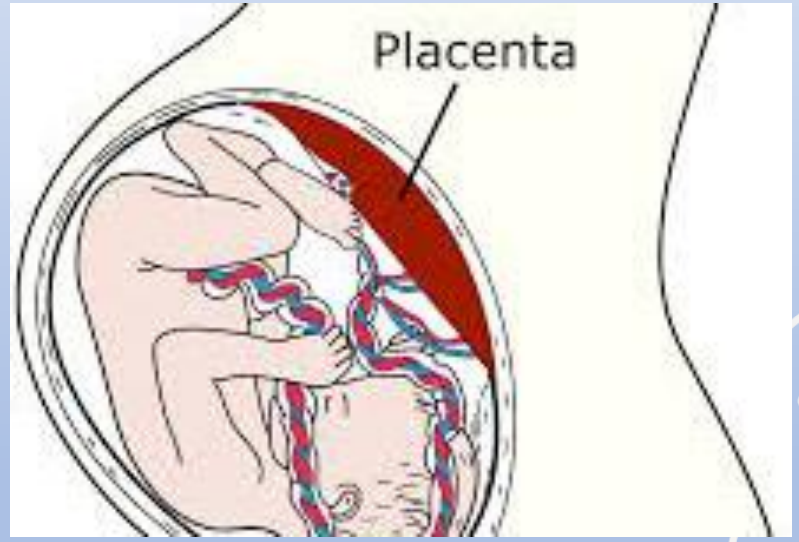
They are small (~40nm diameter), icosahedral, non-enveloped viruses that replicate in the nucleus. Depending on the host cell, they can either transform the cell or replicate the virus and lyze the cell.

SV40 virus, a polyoma virus

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

Route of transmission

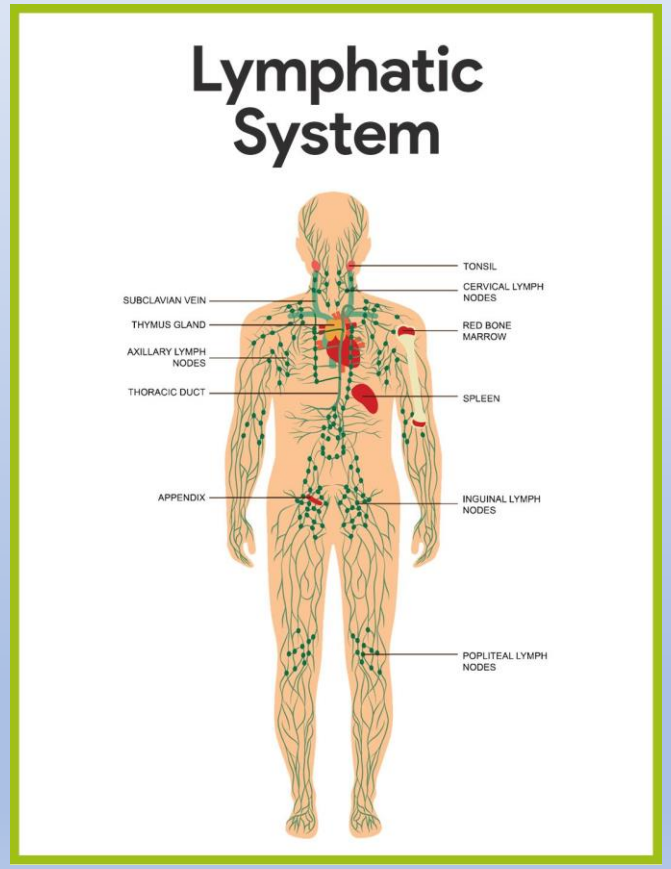


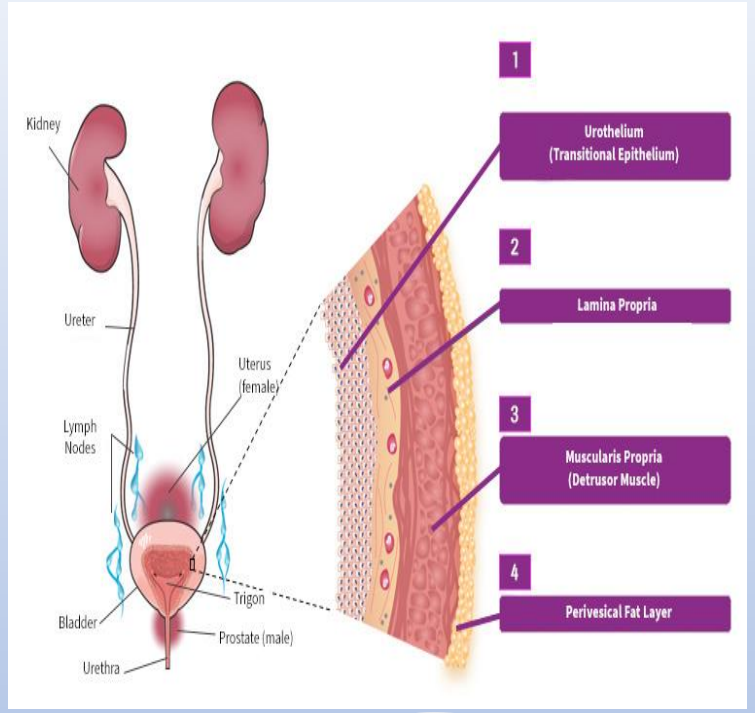


Bohl DL, Brennan DC. BK virus nephropathy and kidney transplantation. Clinical Journal of the American Society of Nephrology. 2007;2(Supplement 1):S36-S46

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





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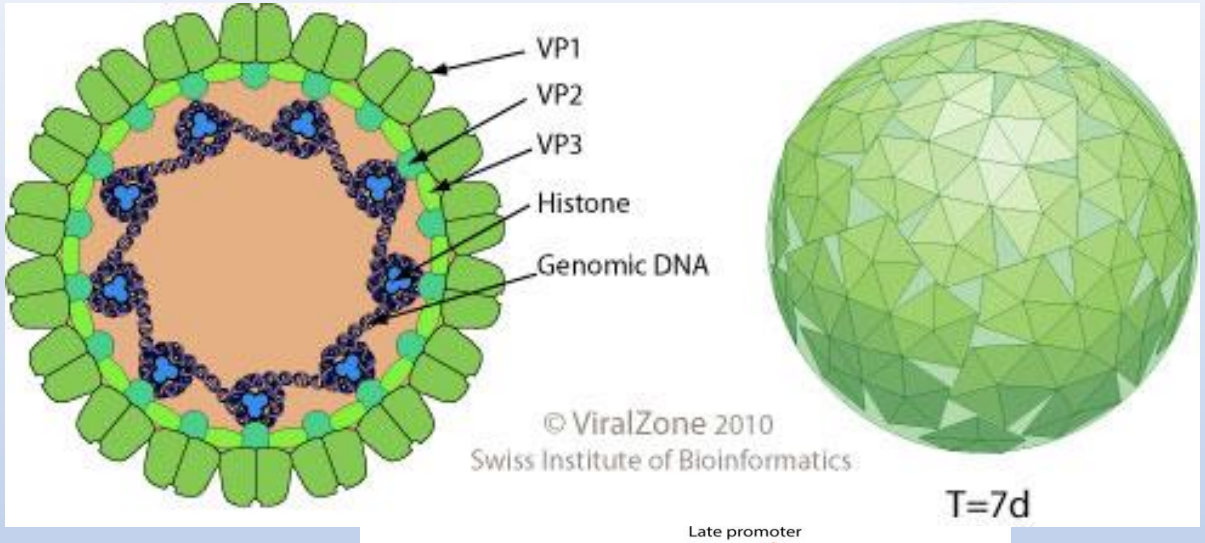
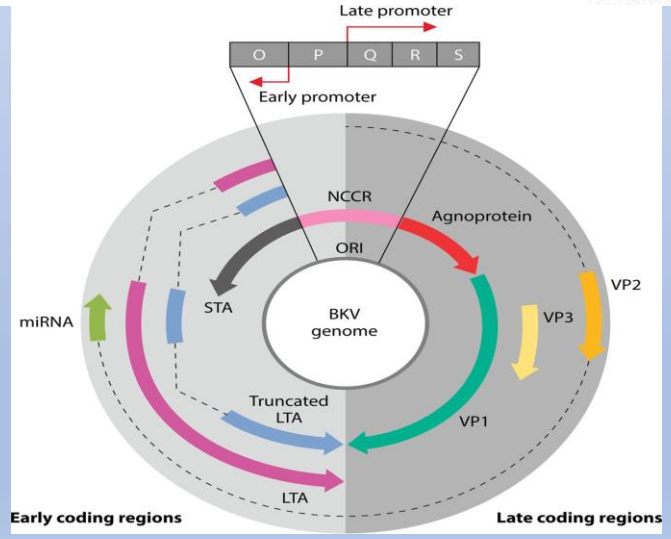
The BK virus was first isolated from the urine of a renal transplant recipient with ureteric stenosis in 1971, but it was not until 20 years later that BK was recognized as a cause of interstitial nephritis and allograft failure in renal transplant recipient.

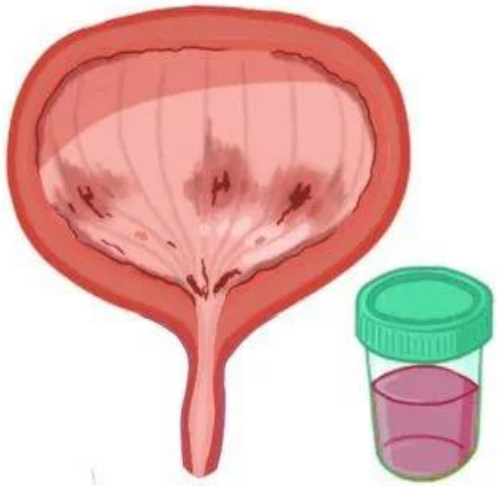




- BK virus infection: an update on diagnosis and treatment
- Deirdre Sawinski and Simin Goral
- Nephrol Dial Transplant (2015) 30: 209–217 doi: 10.1093/ndt/gfu023
Factors and outcome in BK virus nephropathy in a Hispanic kidney transplant population D. Pe´rez-Torres, J. Bertra´n-Pasarell,E, et al.
- Transplant Infectious Disease 2010: 12: 16-22

BK VIRUS (BKV)

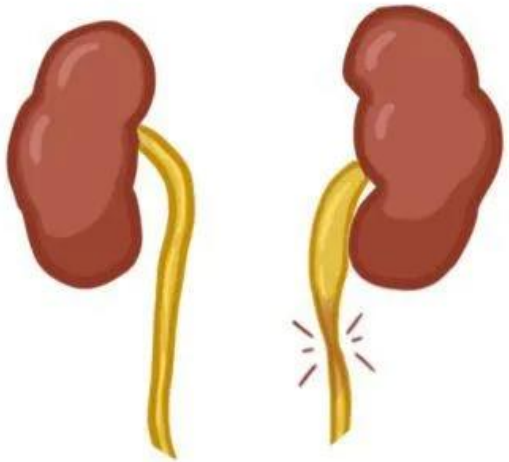
CLINICAL MANIFESTATIONS



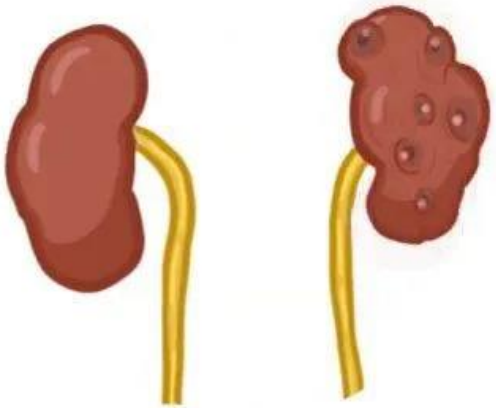
HEMORRHAGIC CYSTITIS

↳ BLOODY URINE

↳ BONE MARROW TRANSPLANT RECIPIENTS

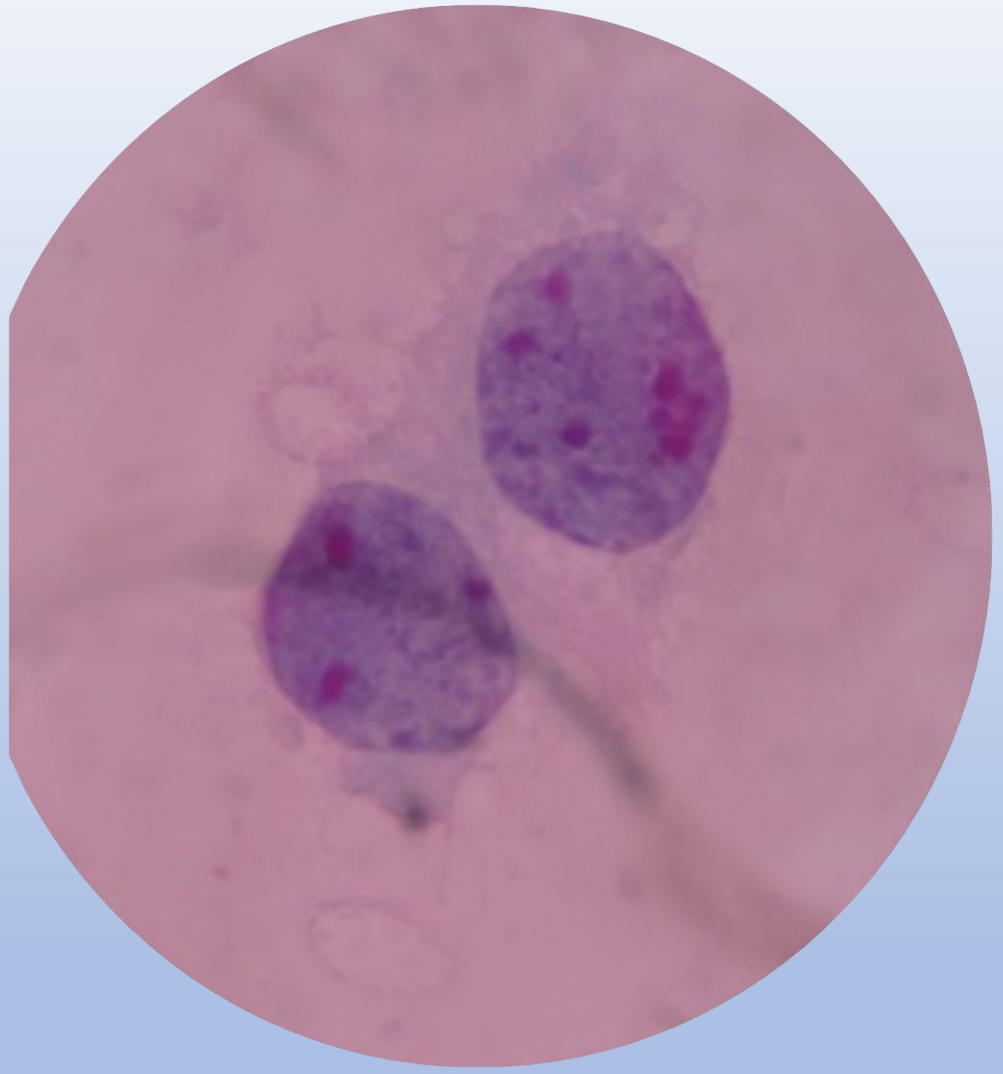


URETERAL STENOSIS



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

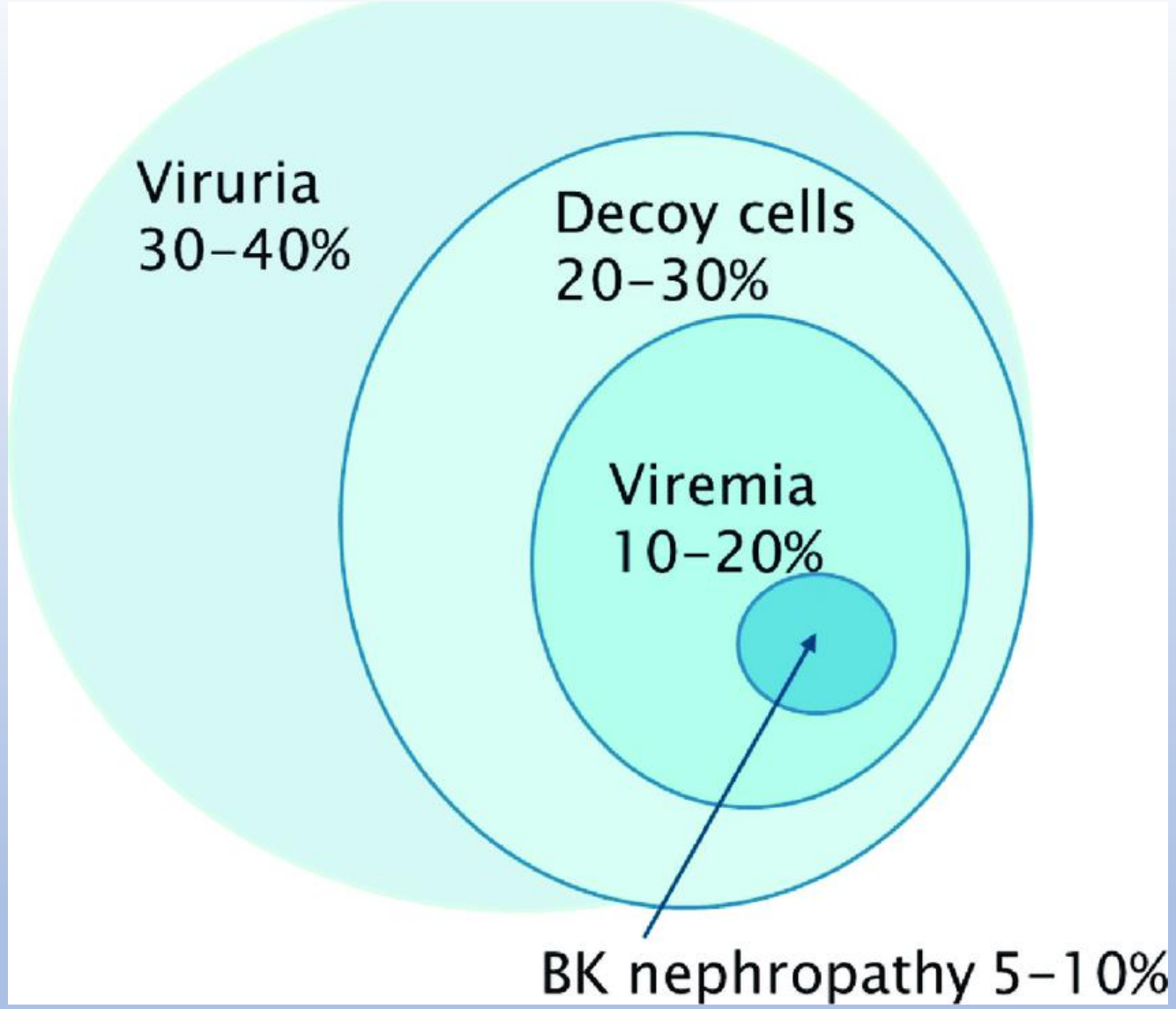
- Influence of surveillance renal allograft biopsy on diagnosisand prognosis of polyomavirus-associated nephropathyCHRISTOPHER K. BUEHRIG, DONNA J. LAGER, MARK D. STEGALL, MICHELLE A. KREPS,WALTER K. KREMERS, JAMES M. GLOOR, THOMAS R. SCHWAB, et al. Kidney International, Vol. 64 (2003), pp. 665–673

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.



Natural course of BKVAN

Type and prevalence of BKV infections in KTRs.

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

BK Virus Nephropathy and Kidney Transplantation
Daniel Bohl- Daniel C. Brennan
Clin J Am Soc Nephrol 2: S36-S46,2007

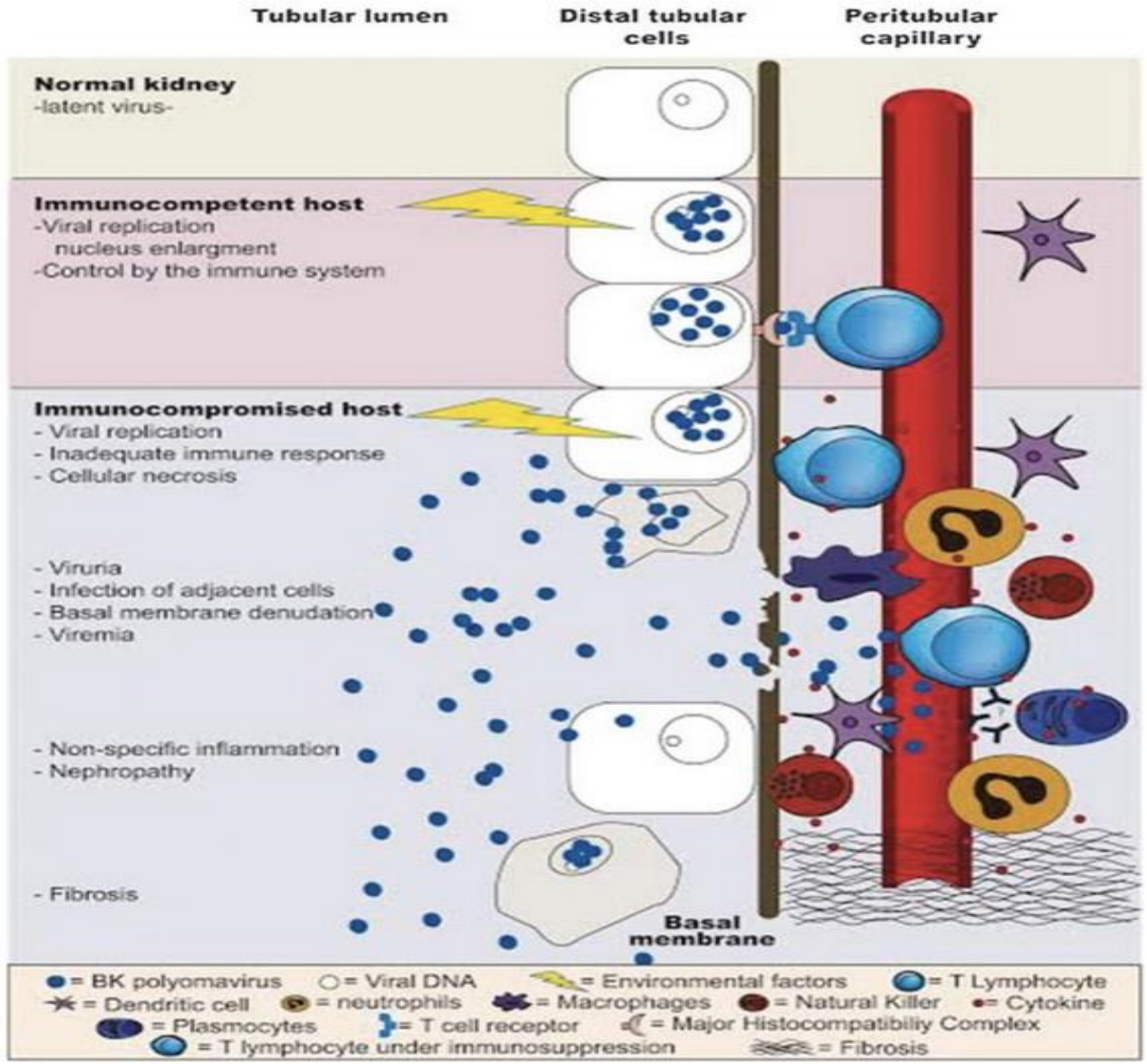
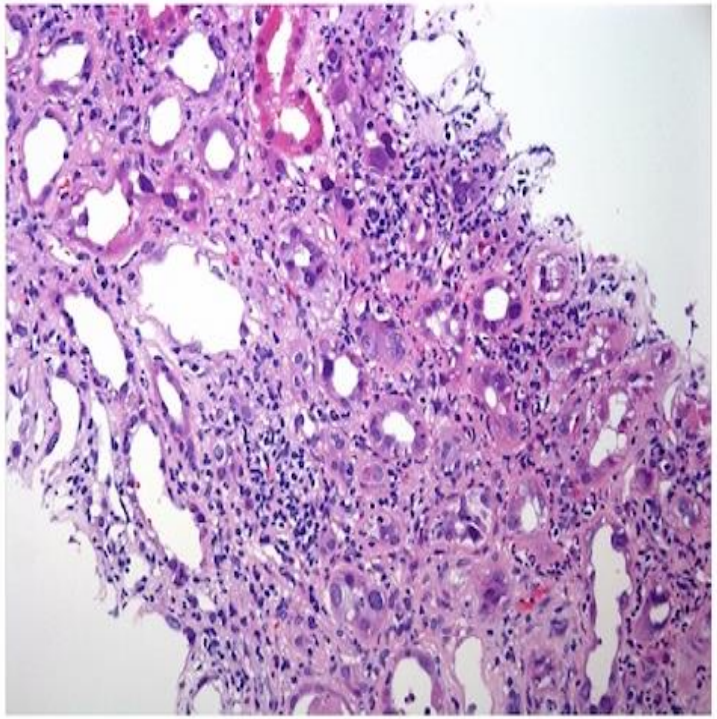


FIGURE 2. Physiopathology of PVAN. Depiction of PVAN development form latency in the uroepithelium (top) to the development of renal inflammation and fibrosis (bottom).

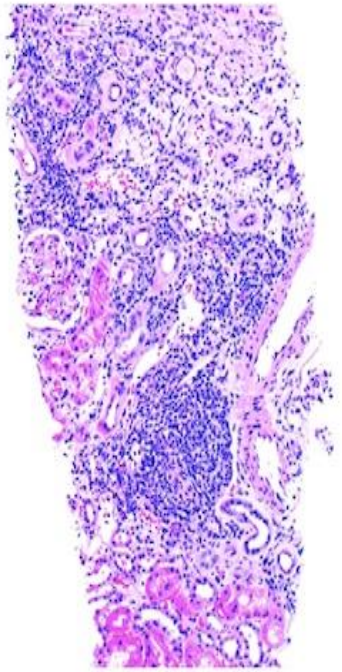
Lamarche C, Orio J, Collette S, Senécal L, Hébert M-J, Renoult É, et al. BK polyomavirus and the transplanted kidney: immunopathology and therapeutic approaches. Transplantation. 2016;100(11):2276

inflammation. Image courtesy of Arkana Labs.



Viral cytopathic effect (very rare)

Image 7. Viral cytopathic effect and interstitial



Corticomedullary junction inflammation

Image 8. Corticomedullary junction inflammation. Image courtesy of Arkana Labs

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

Obesity (Hypoperfusion, ischemia, longer operation time)
Vit D < 30 ng

Management of BKPolyomavirus Infection inKidney and Kidney-PancreasTransplant RecipientsA Review ArticleNissreen Elfadawy, MS, MDa,, Masaaki Yamada, MDb,Nagaraju Sarabu, MD Infect Dis Clin N Am 32 (2018) 599–613.

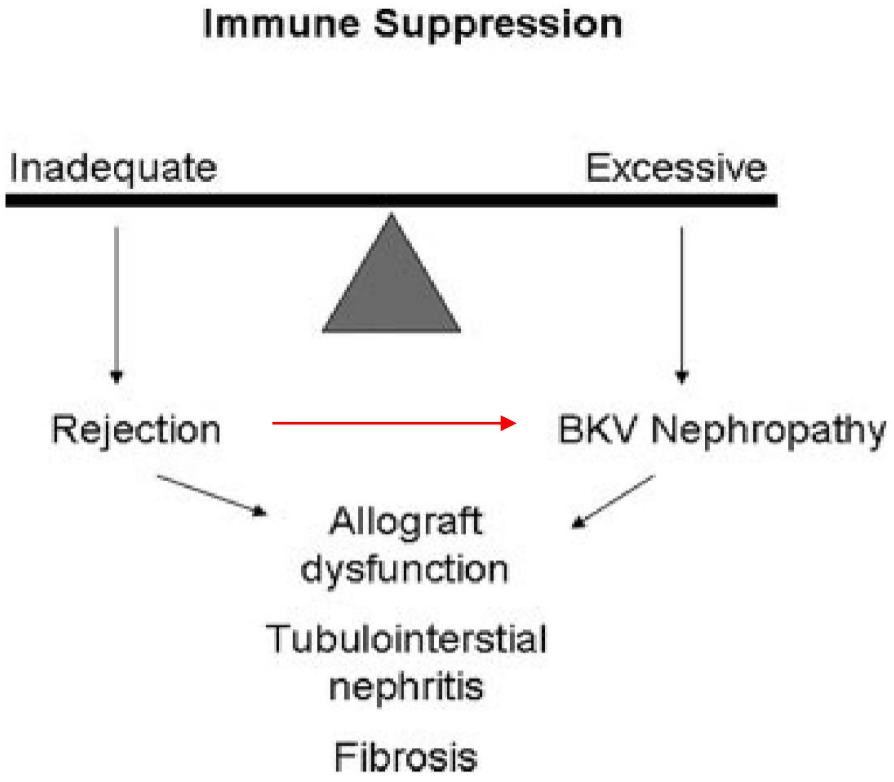


Figure 3. Impaired immune suppression balance. Inadequate immune suppression results in rejection, whereas excessive immune suppression results in BKV nephropathy. Both conditions present as allograft dysfunction with tubulointerstitial nephritis and progression to fibrosis.

- 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

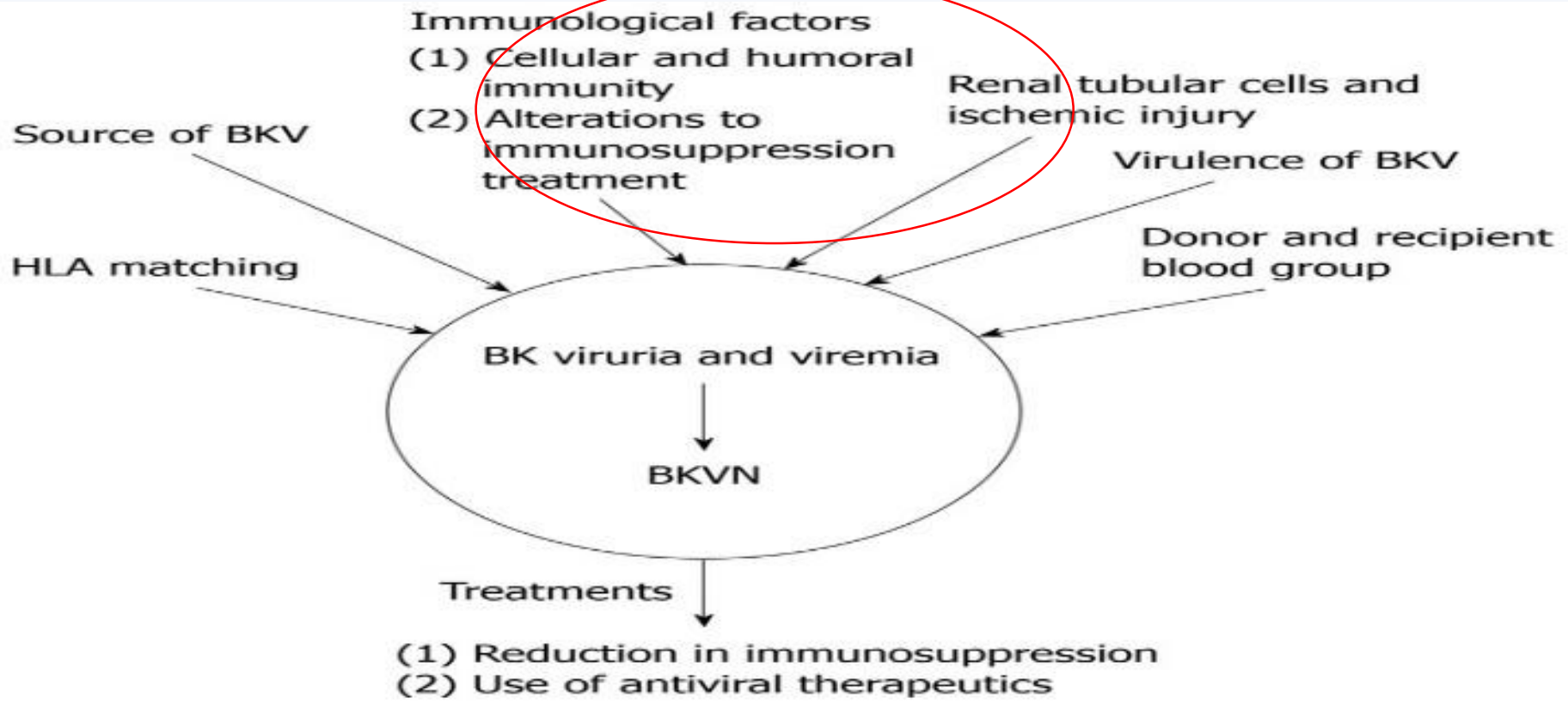


Figure 1 Proposed mechanisms for the pathogenesis of BK virus-associated nephritis after BK virus infection has occurred resulting in BK viruria or BK viremia. These mechanisms include immunological factors, such as alterations to immunosuppressive therapy and cellular and humoral immunity, the source 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

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

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.

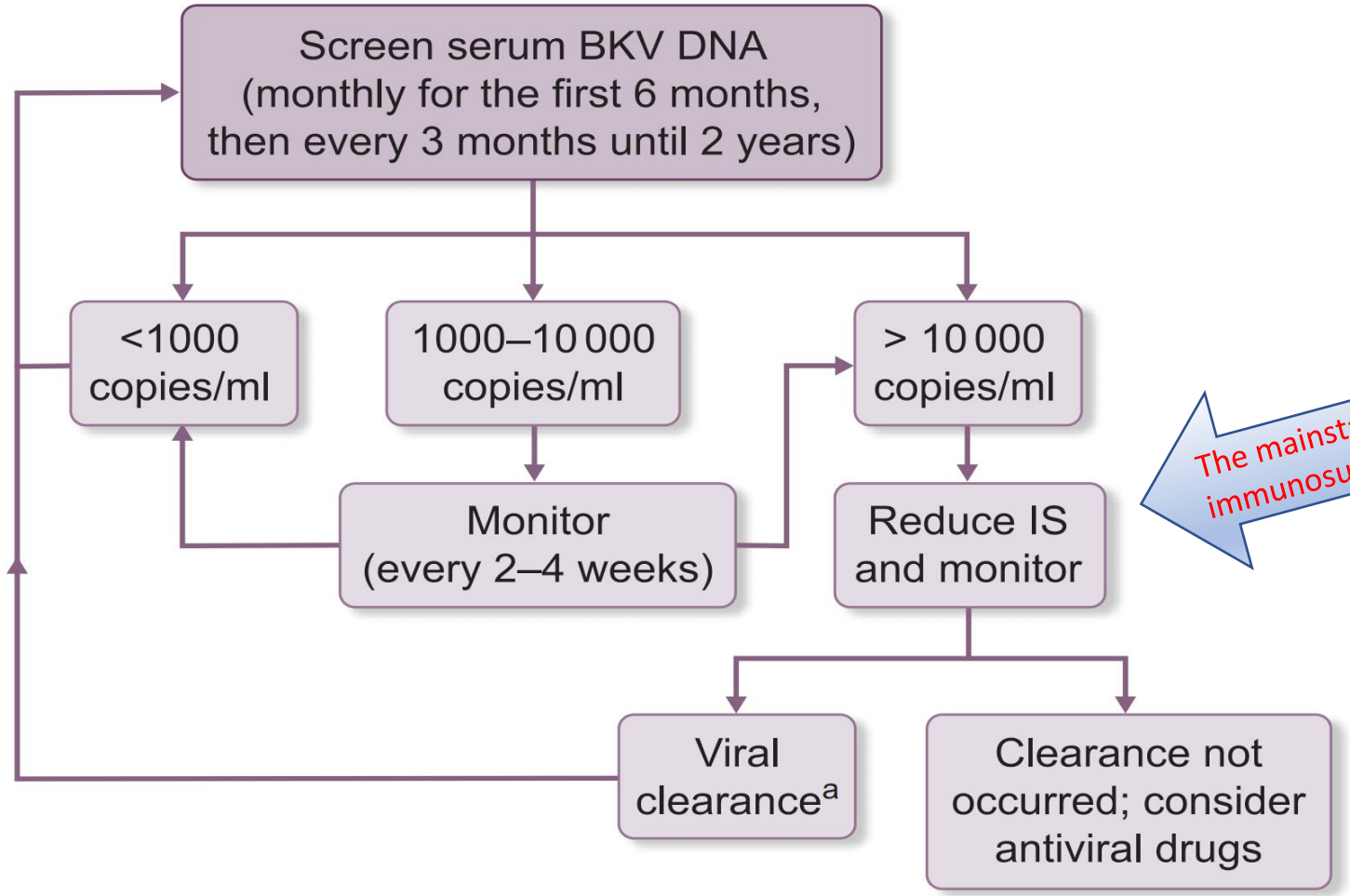
- ✓ Pérez-Torres D, Bertrán-Pasarell J, Santiago-Delpín E, González-Ramos M, Medina-Mangual S, Morales-Otero L, et al. Factors and outcome in BK virus nephropathy in a Hispanic kidney transplant population. Transplant Infectious Disease. 2010;12(1):16-22
- ✓ Sharma R, Zachariah M. BK Virus Nephropathy: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

Nephrol Dial Transplant (2021) 36: 985–987
doi: 10.1093/ndt/gfz214
Advance Access publication 7 November 2019

ndt digest

Risk factors, pathogenesis, presentation and management of BK virus infection in kidney transplantation

Erol Demir, Aydin Turkmen and Mehmet Sukru Sever
Department of Internal Medicine, Division of Nephrology, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey



The mainstay of treatment of PVN is immunosuppression reduction.

FIGURE 1: Algorithm for screening and management of BKVN. Adapted from references [1] and [9]. [a]Viral clearance has been defined as <1000 copies/mL or undetectable levels.

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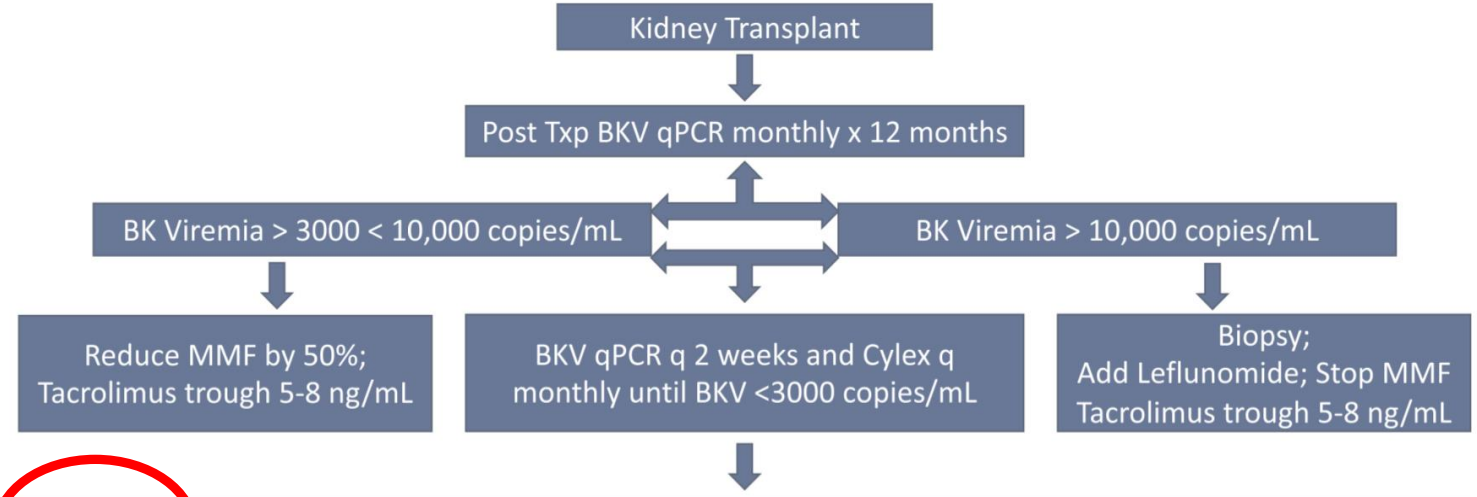


Cylex	BKV qPCR (copies/mL)		
	< 3,000	**3000 – 10,000**	**> 10,000**
< 225	Resume Baseline IS	Reduce MMF by 50%; Tacrolimus trough 5-8 ng/mL	Add Leflunomide; Stop MMF Tacrolimus trough 5-8 ng/mL
225 - 500	Resume Baseline IS	Reduce MMF by 50%; Tacrolimus trough 8-10 ng/mL	Leflunomide; Reduce MMF by 50%; Tacrolimus trough 5-8 ng/mL; Cidofovir if refractory
> 500	Resume Baseline IS	Leflunomide; Reduce MMF by 50%; Tacrolimus trough 8-10 ng/mL; Cidofovir if refractory	Leflunomide; Reduce MMF by 50%; Tacrolimus trough 8-10 ng/mL; Cidofovir if refractory

Figure 1 Monitoring and treatment protocol for BK viremia at our center.

Cylex: measure the concentration of ATP from circulating CD4 cells following in vitro stimulation with phytohemagglutinin (PHA) as an indicator of immune cell function.

BK Virus Nephropathy: Prevalence,Impact and Management Strategies

American Journal of Transplantation 2016; 16: 821–832
Wiley Periodicals Inc.

doi: 10.1111/ajt.13541

BK Polyomavirus Replication in Renal Tubular Epithelial Cells Is Inhibited by Sirolimus, but Activated by Tacrolimus Through a Pathway Involving FKBP-12

H. H. Hirsch[1,2,3,*], K. Yakhontova[1], M. Lu[1] and J. Manzetti[1]

[1]Transplantation & Clinical Virology, Department of Biomedicine (Haus Petersplatz), University of Basel, Basel, Switzerland
[2]Division Infection Diagnostics, Department of

Abbreviations: BKPyV, BK polyomavirus; CsA, cyclosporine A; EVGR, early viral gene region; FKBP-12, FK binding protein 12kda; KT, kidney transplantation; LTag, large T-antigen; LVGR, late viral gene region; sTag, small T-antigen; SIR, sirolimus; TAC, tacrolimus; VP1, viral capsid protein 1

Hirsch et al

Cyclosporine A also inhibited BKPyV replication,
while tacrolimus activated BKPyV replication.

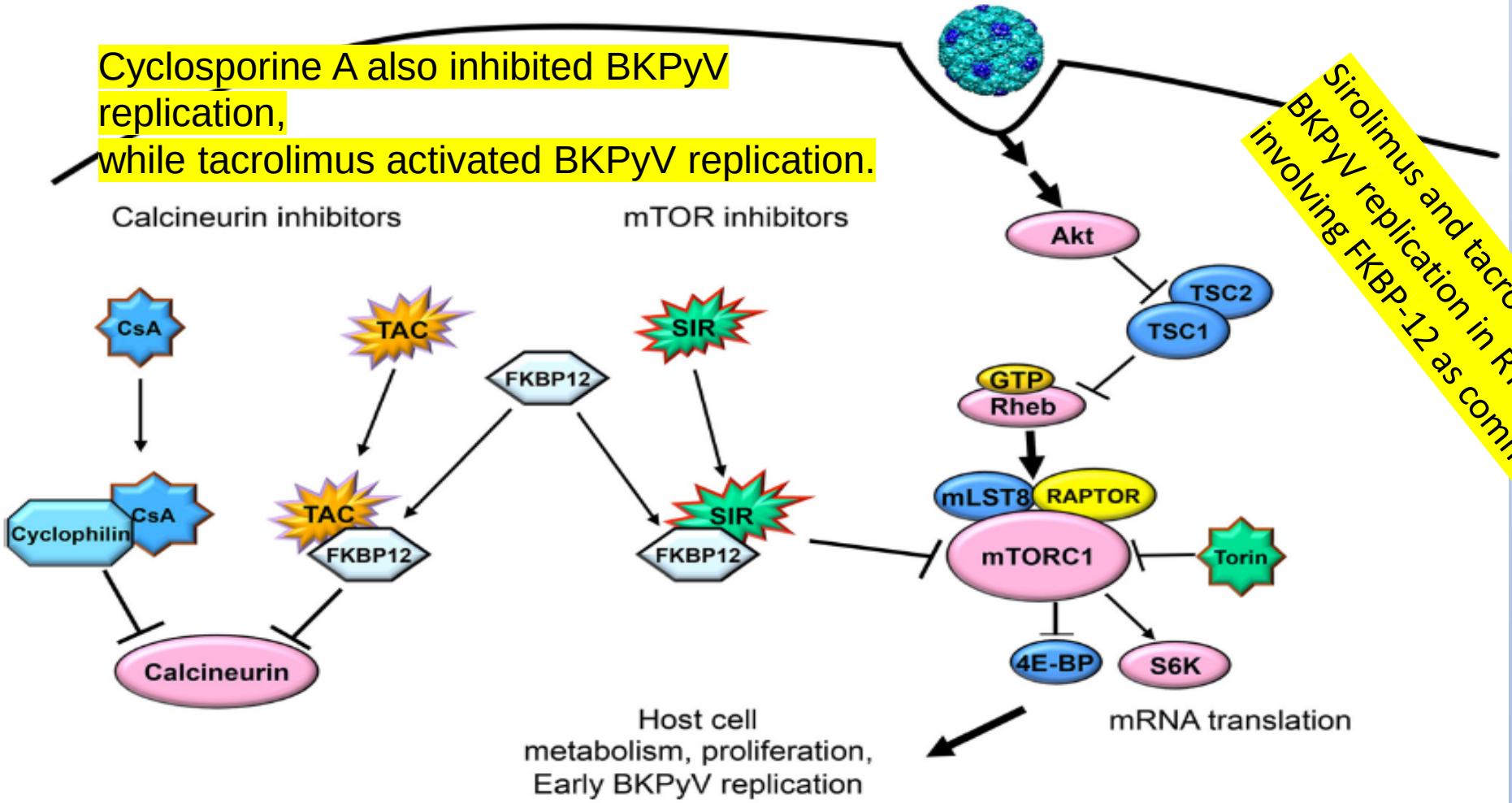


Figure 9: Effects of calcineurin inhibitors and mTOR inhibitors on BKPyV replication. Akt, plasma membrane located, inositol-activated serine-threonine kinase; BKPyV, BK polyomavirus; CsA, cyclosporine A; FKBP, FK binding protein; mTOR, mammalian target of rapamycin; mTORC1, mammalian target of rapamycin complex 1; SIR, sirolimus; S6K, S6 kinase; TAC, tacrolimus; TSC, tuberous sclerosis factor; 4E-BP, translation inhibitor 4E binding protein.

Sirolimus and tacrolimus exert opposite effects on BKPyV replication in RTE cells by a mechanism involving FKBP-12 as common target

Sirolimus impaired BKPyV replication with a 90% inhibitory concentration of 4 ng/mL by interfering with mTOR–SP6-kinase activation.

The Journal of Infectious Diseases

MAJOR ARTICLE

Sirolimus and Other Mechanistic Target of Rapamycin Inhibitors Directly Activate Latent Pathogenic Human Polyomavirus Replication

Jennifer Alvarez Orellana,[1,2] Hyun Jin Kwun,[1,3] Sara Artusi,[2] Yuan Chang,[1,4,a] and Patrick S. Moore[1,2,a]

[1]Cancer Virology Program, Hillman Cancer Center, Pittsburgh, Pennsylvania, USA, [2]Department of Microbiology and Molecular Genetics, University of Pittsburgh, Pittsburgh, Pennsylvania, USA, [3]Department of Microbiology and Immunology, Pennsylvania State University, Hershey, Pennsylvania, USA, and [4]Department of Pathology, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

Table 1 Anti-Virals for PVN

Anti-Virals			
Name	**Class/Mechanism**	**Dose**	**Comments**
Leflunomide[49–52]	Anti-Inflammatory; Anti-Viral; Immunosuppressive	PO: Loading- 100 mg daily for 3–5 days; maintenance- 20-60 mg qD; Trough Level –50-100 μg/mL	Can be used following discontinuation of MMF.
Cidofovir[53–55]	Nucleoside analog	IV: 0.25–1.0 mg/Kg at 1–3 weeks	Used in refractory cases; Nephrotoxicity is the most serious adverse effect.
Brincidofovir[56,57]	Investigational Prodrug of Cidofovir; Anti-viral activity	PO: 2 mg/Kg twice weekly	Reasonably well tolerated; Investigational.
Intravenous immunoglobulin (IVIG)[58–61]	Immunoglobulin preparation with high titers of neutralizing antibodies to BK virus	IV: 0.25–2.0 g/Kg	Can be used as an adjunct to other measures in refractory cases.
Levofloxacin[62–64]	Fluoroquinolones; Antiviral, inhibit helicase activity of large T antigen	PO: 500 mg qD (renally adjusted)	Levofloxacin failed to show benefit in randomized controlled trials.
Everolimus[47,48]	Inhibits mammalian target of rapamycin (mTOR) kinase activity, inhibiting T and B lymphocyte activation and proliferation.	PO 0.75 mg twice daily adjusted to trough levels of 3–8 ng/mL.	Can be used following discontinuation of MMF. Limited literature supporting its use.

Received: 3 July 2020 | Revised: 11 August 2020 | Accepted: 28 August 2020

DOI: 10.1111/tid.13465

CASE REPORT

Transpl. Infect. Dis. 2021;23:e13465. WILEY

Resurgence of BK virus following Covid-19 in kidney transplant recipients

Christophe Masset[1] | Simon Ville[1,2] | Franck Halary[2] | Benjamin Gaborit[3] | Celine Bressolette-Bodin[4] | Clément Deltombe[1] | Amaury Dujardin[1] | Lola Jacquemont[1,2] | Sabine Lebot[1] | Delphine Kervella[1,2] | Lucille Figueres[1,2] | Diego Cantarovich[1] | Magali Giral[1,2] | Maryvonne Hourmant[1,2] | Gilles Blancho[1,2] | Claire Garandeau[1] | Aurélie Meurette[1] | Jacques Dantal[1,2]

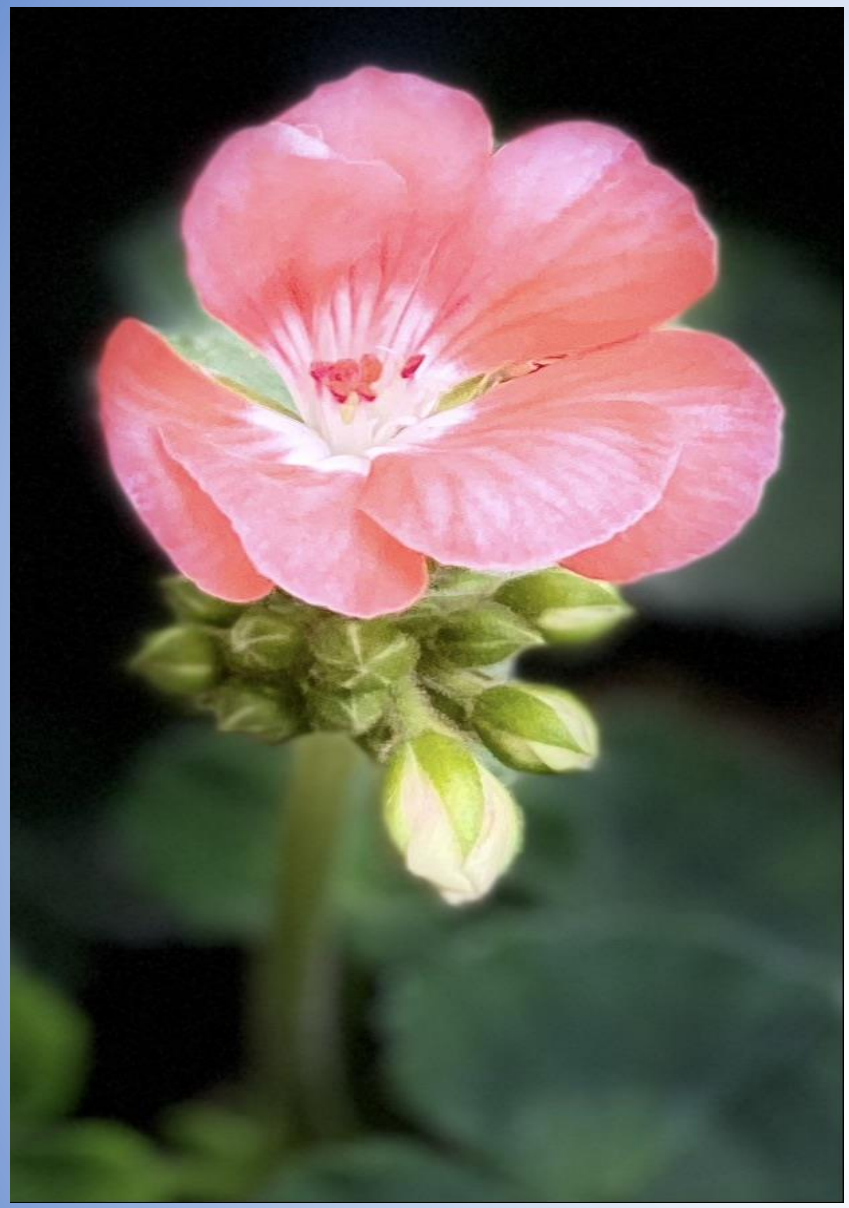
Outcomes of kidney retransplantation after graft loss as a result of BK virus nephropathy in the era of newer immunosuppressant agents

Am J Transplant. 2020;20:1334–1340

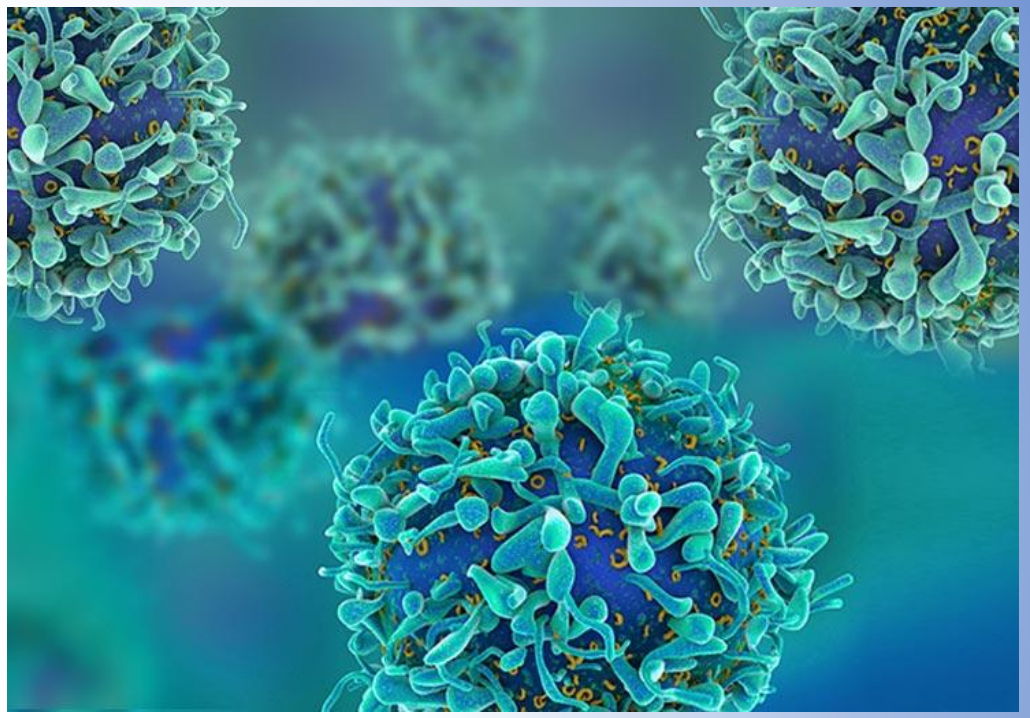
Current guidelines have recommended the achievement of BK viral clearance before retransplant among patients who developed prior allograft failure as a result of BKVAN.

The rationale is that the risk of recurrent BK infection is increased in patients who failed to achieve clearance of BK viremia (undetectable BK viral load) before retransplant.

Our study found that patients who underwent retransplant for BKVAN had a longer waiting time.



They are everywhere, take care.



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Journal of Pharmaceutical Care
jpc.tums.ac.ir

Novel Immunological Aspects of Sirolimus as a New Targeted Therapy for COVID-19

Mahshid Naserifar*, Hesamoddin Hosseinjani*

* Department of Clinical Pharmacy, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran.

Received: 2020-06-25, Revised: 2020-07-06, Accept: 2020-07-07, Published: 2020-09-30

According to reports, viral protein expression and virion release have been effectively blocked by sirolimus which is an inhibitor of mammalian target of rapamycin (mTOR).

Journal of Research in Clinical Medicine

J Res Clin Med, 2020, 8: 44
doi: 10.34172/jrcm.2020.044
https://jrcm.tbzmed.ac.ir

TUOMS PRESS

Letter to Editor

Sirolimus to treat SARS-CoV-2 infection: an old drug for a new disease

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[1]AOU San Giovanni di Dio e Ruggi D'Aragona, Department of Anaesthesia and Intensive Care, Via San Leonardo, 1, 84131, Salerno, Italy
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Received: 26 Dec. 2020 Accepted: 9 Nov. 2020 e-Published: 28 Nov. 2020

Appelberg et al demonstrated that SARS-CoV-2 causes excessive activation of the mammalian target of rapamycin (mTOR) signaling pathway in an in vitro model.

Trends in Transplant, 2020, vol 13: 1-10

Table 3. Potential Risk factors associated with an increased risk of post-transplant BKV re-activation

Transplant-related:

Immunosuppression

- Induction therapy (ATG)
- Type and degree of immunosuppression

Graft-related

- Prior treatment of acute rejection
- Prolonged cold/warm ischemia timing
- Delayed graft function
- Ureteric stent placement
- Renal injury (immune related,.. etc.)

Donor-related:

- Older donor age
- Donor BK virus seropositivity
- Degree of HLA matching
- ABO-Incompatibility
- Absence of HLA-C7
- Donor status (deceased versus living donor)

Recipient-related:

- Older recipient Age>50
- Gender (male recipient)
- Recipient race
- Obesity (BMI>30 kg/m^2)
- Previous graft loss due to BK nephropathy
- Diabetes mellitus
- BK seronegativity
- HLA mismatching, Absence of HLA-C7, certain HLA alleles
- High PRA titres
- Genetic factors
- Lymphocytes mean percentage (%)
- G-CSF use
- Dialysis Modality pre-transplantation
- CMV status

The Journal of Infectious Diseases
MAJOR ARTICLE

Sirolimus and Other Mechanistic Target of Rapamycin Inhibitors Directly Activate Latent Pathogenic Human Polyomavirus Replication

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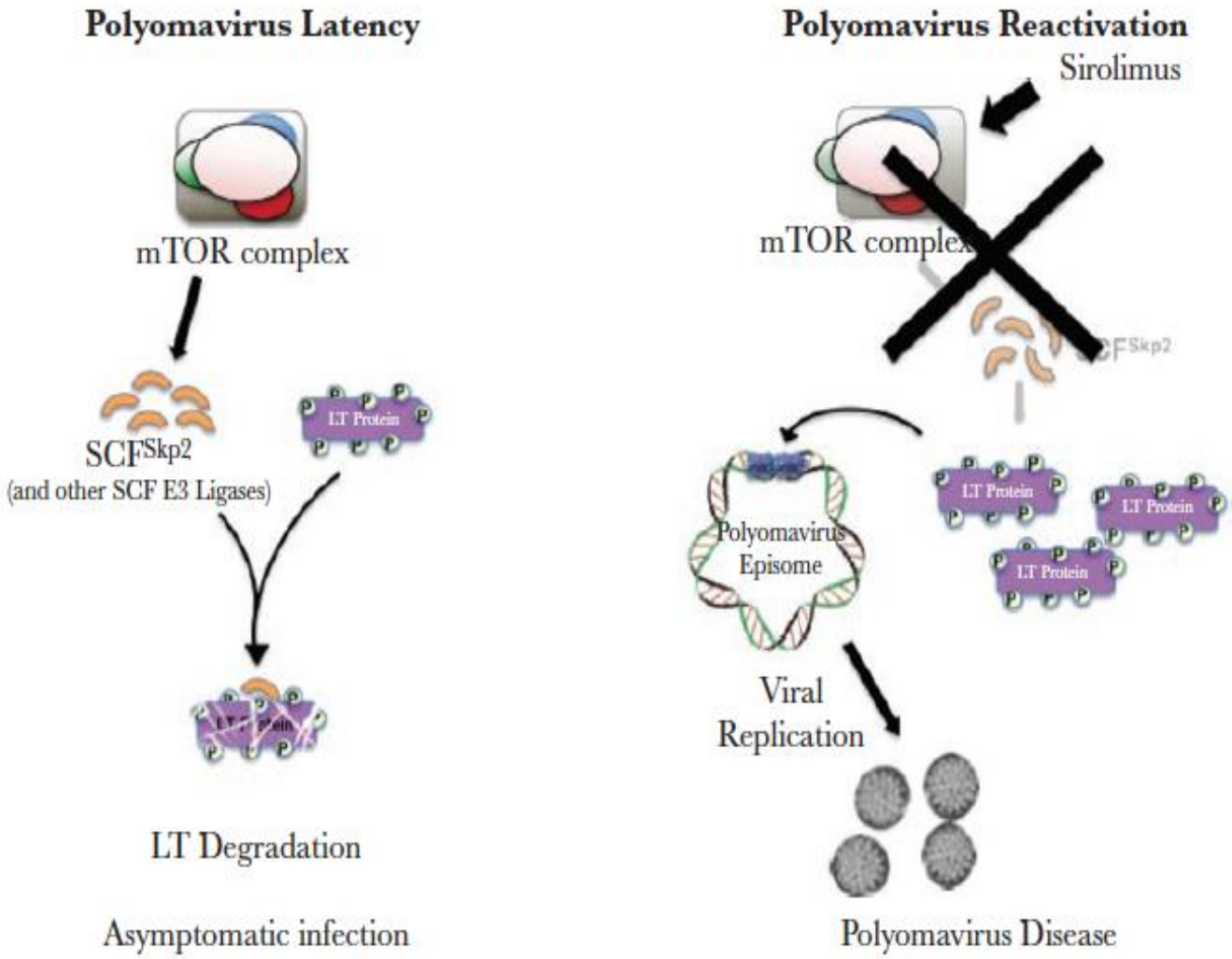
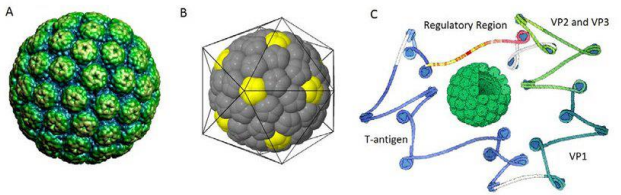


Figure 5. Model for human polyomavirus (HPyV) reactivation in transplant recipients on mechanistic target of rapamycin (mTOR) inhibitor therapy. HPyV large T (LT) proteins are continuously degraded by different E3 ligases, including Skp2. mTOR inhibition negatively regulates Skp2 levels, which results in increased HPyV LT stability and viral replication.

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 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

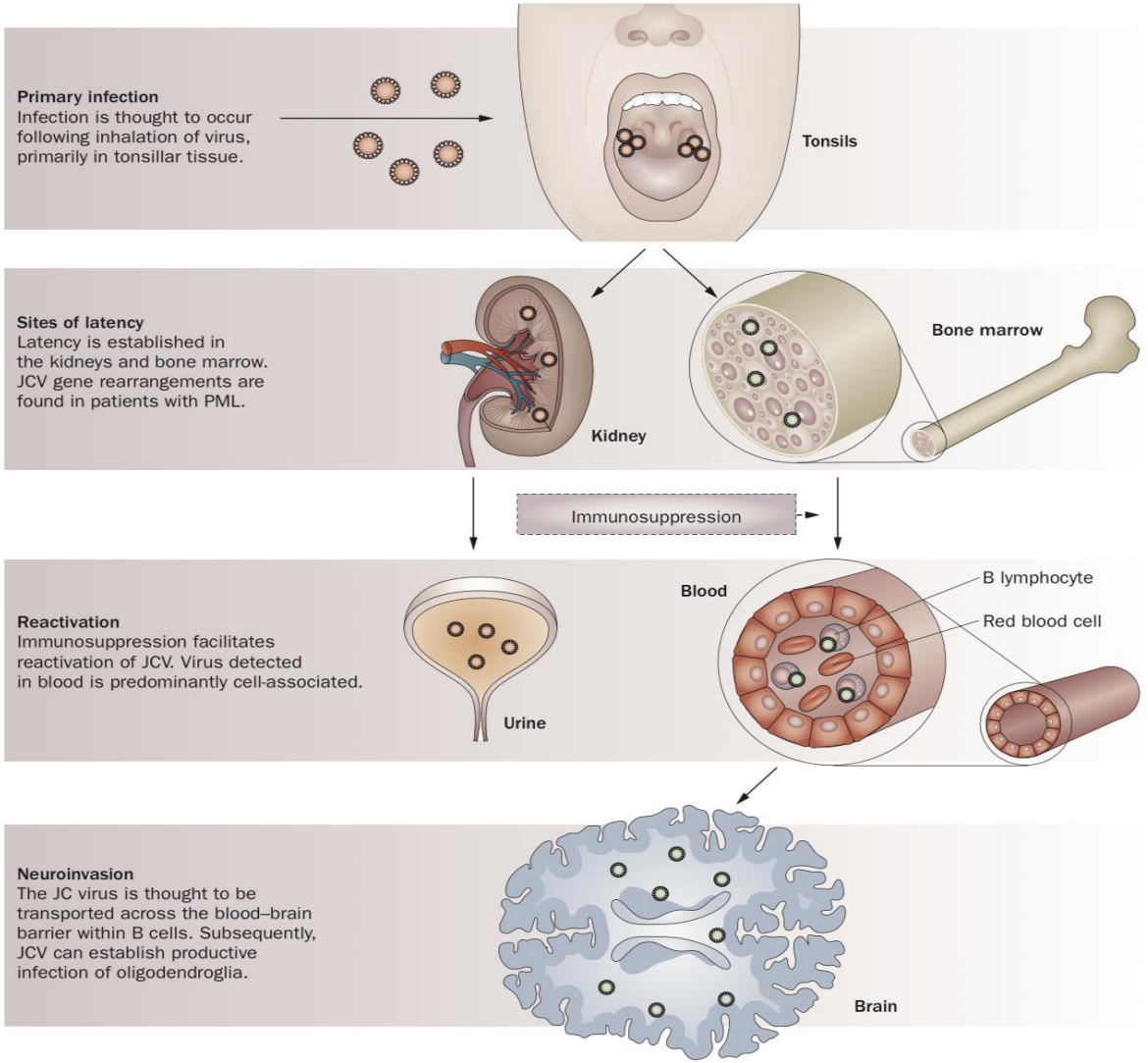


Figure 1 | Proposed disease course of PML. Initial JCV infection is thought to occur in tonsillar tissue after inhalation. Lymphocytes infected with JCV carry virions to the kidney and bone marrow, which are thought to be the primary sites of viral latency. Following reactivation of JCV, the virus is 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

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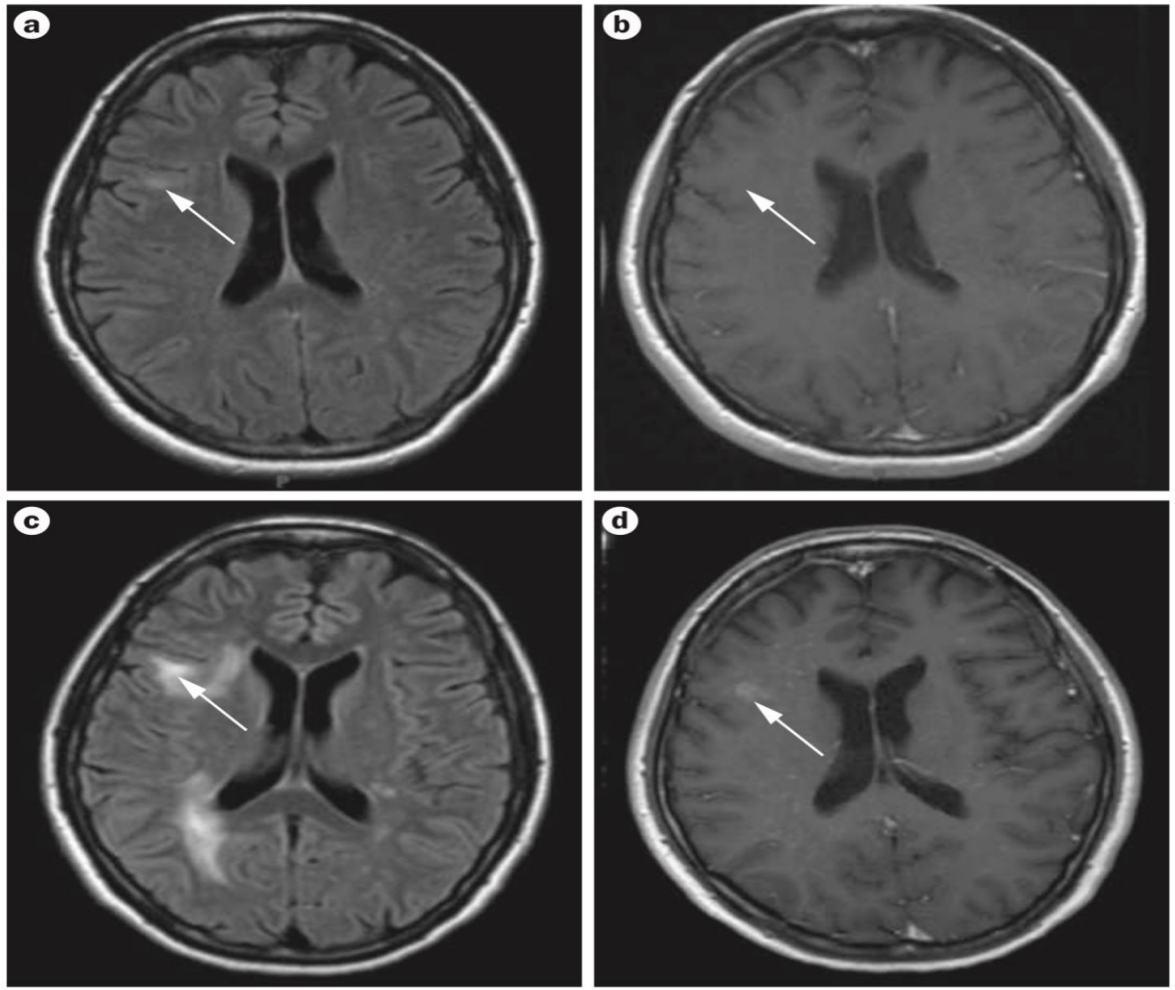

Figure 2 | FLAIR images showing progression of progressive multifocal leukoencephalopathy immune reconstitution inflammatory syndrome. **a** | Multifocal, high-signal-intensity lesions (arrow) in the right hemisphere of a patient after prolonged immunosuppressive therapy for a lung transplant. The cerebrospinal 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.

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 by genotype IV (15%).

- Management of BKPolyomavirus Infection inKidney and Kidney-PancreasTransplant RecipientsA Review ArticleNissreen Elfadawy, MS, MDa,, Masaaki Yamada, MDb,Nagaraju Sarabu, MD Infect Dis Clin N Am 32 (2018) 599–613.

- 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

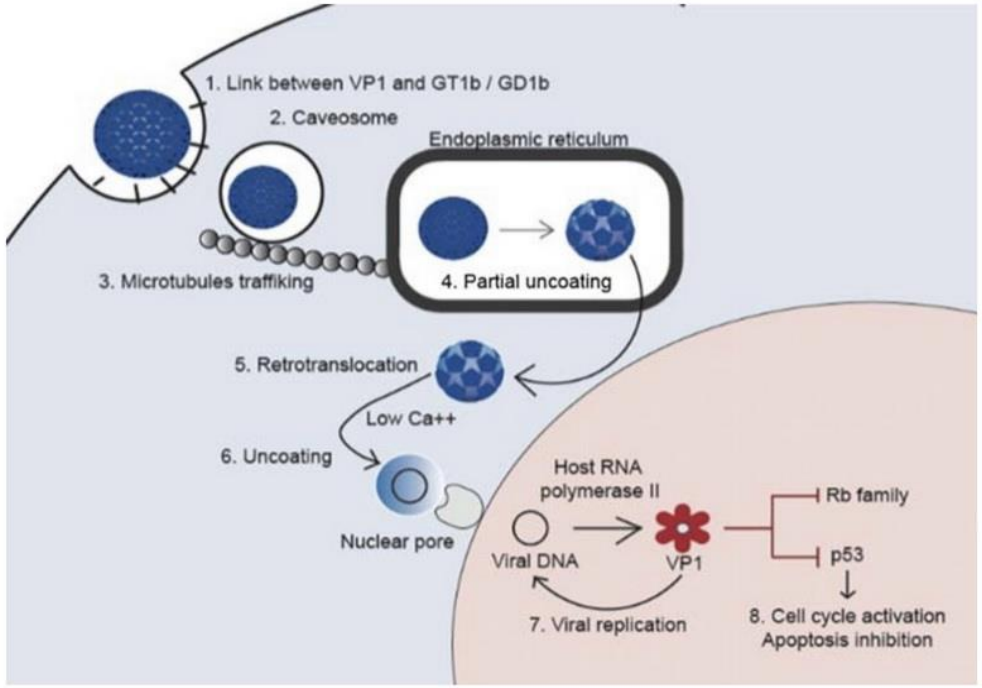

FIGURE 1. BK polyomavirus cell entry and infection. Representation of mechanisms of viral cell entry, trafficking, and infection highlighting action on the cell cycle machinery.

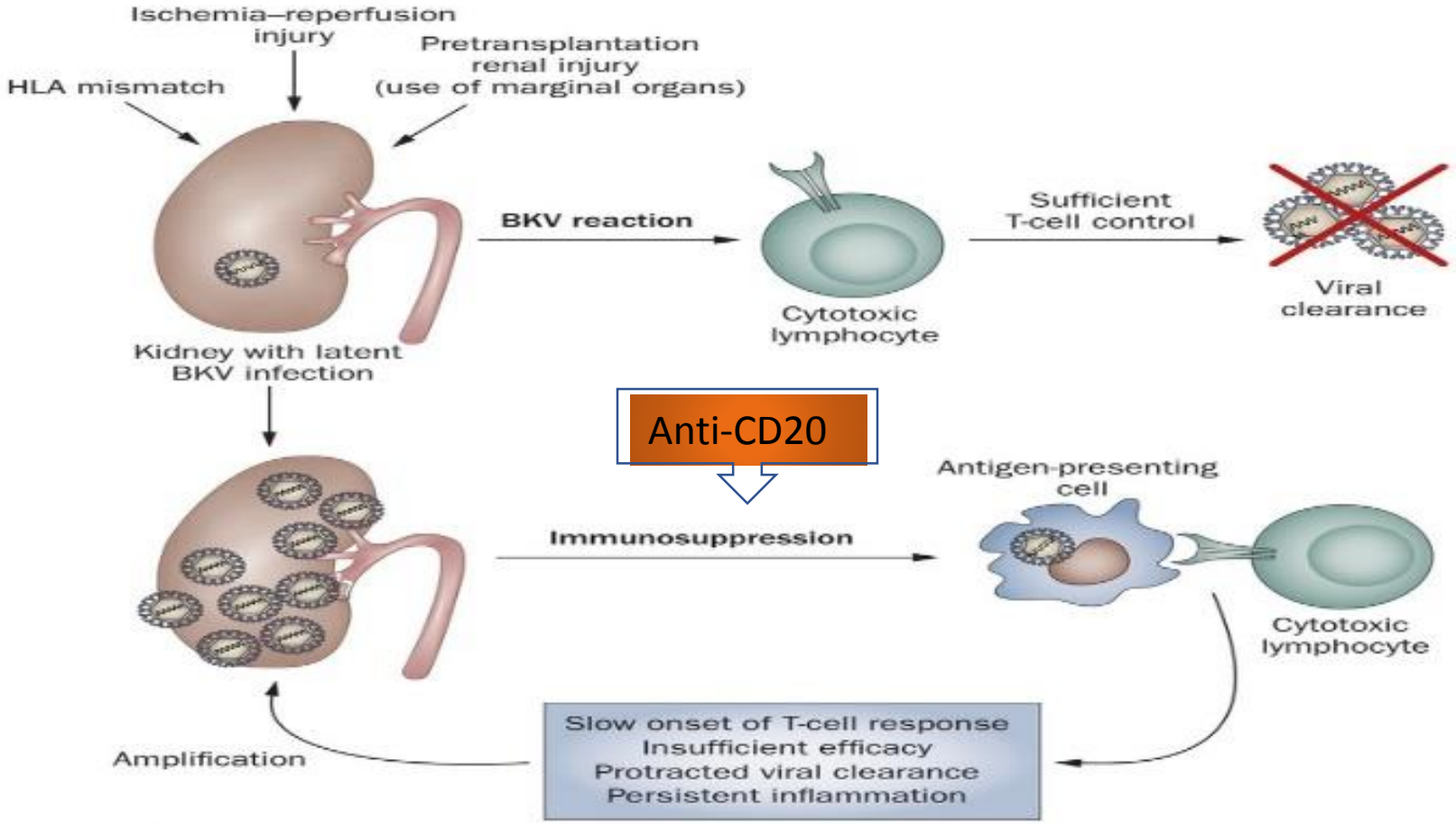

Figure 1 | The functional activity of BKV-specific T cells seems to determine the clinical outcome of BKV reactivation. A sufficient BKV-specific T-cell response is able to control BKV replication and prevent progression of BKV infection to BKVAN. By contrast, insufficient or only partial T-cell-mediated 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