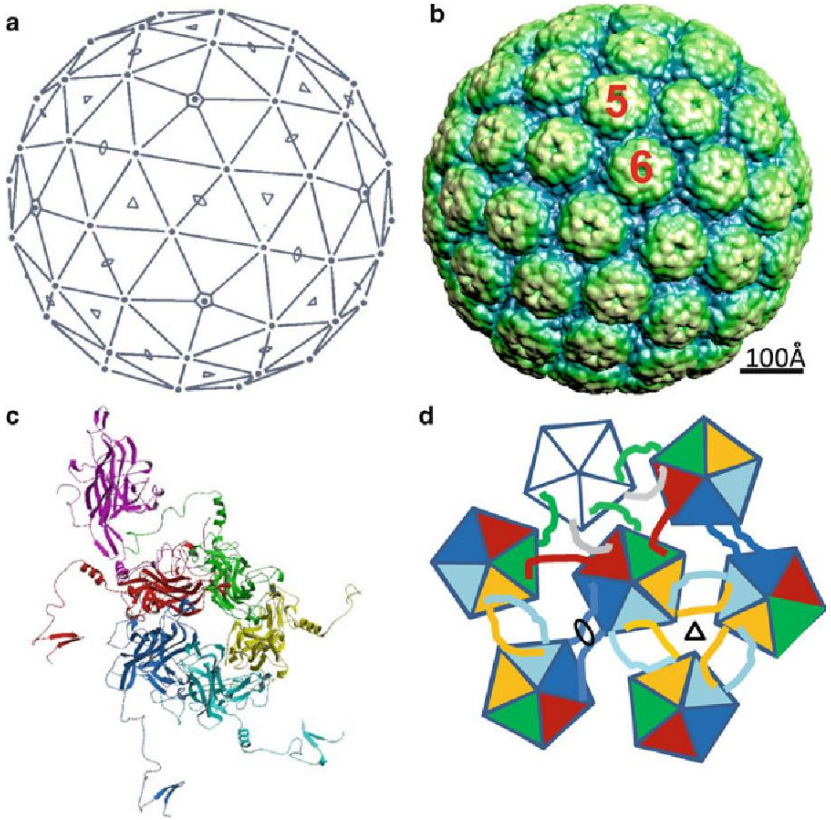
Viral Infections in Renal TX Recipients: BK Virus

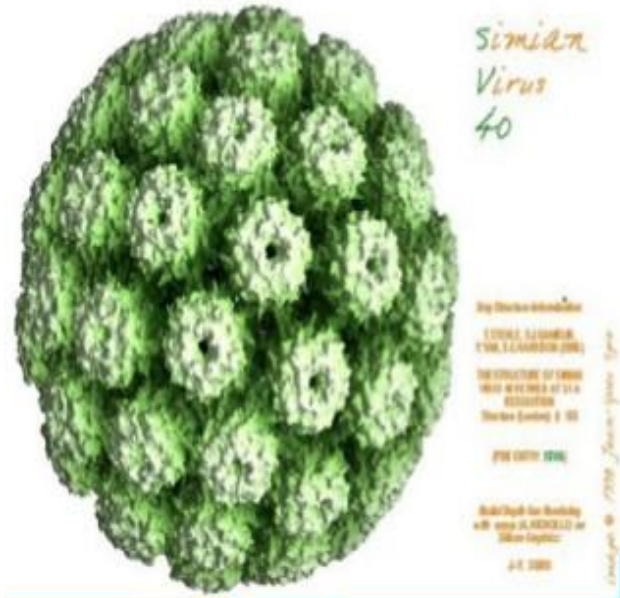
- Masoud Khosravi, M.D., Nephrologist
- Faculty of Guilin University of Medical Sciences
- 000611
- 02 Sep 21

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 1.3 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 sirolimus and mycophenolate mofetil temporarily was discountinued. The patient received IVIG for one week. After 3 month plasma creatinine was 1.4 mg/dL, and blood viremia was cleared.

Polyomaviruses Family



POLYOMAVIRUSES



These include SV40, BK, JC and polyoma viruses.

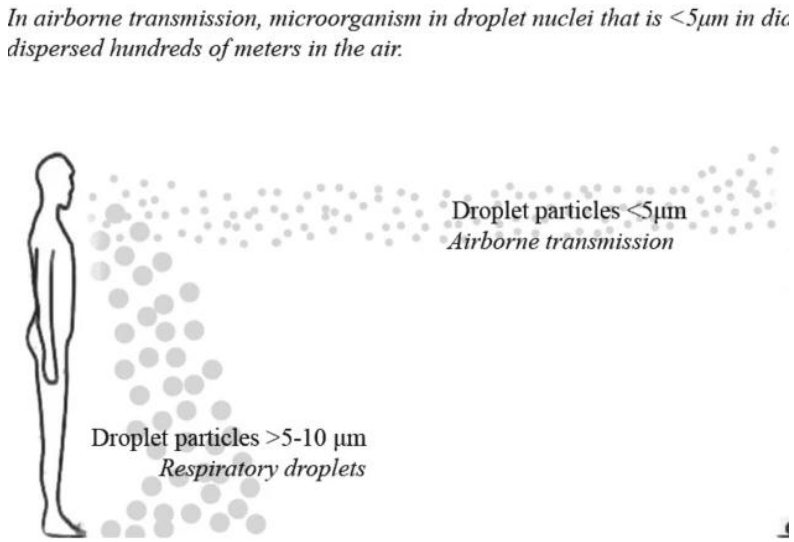
All have a similar strategy for DNA replication.

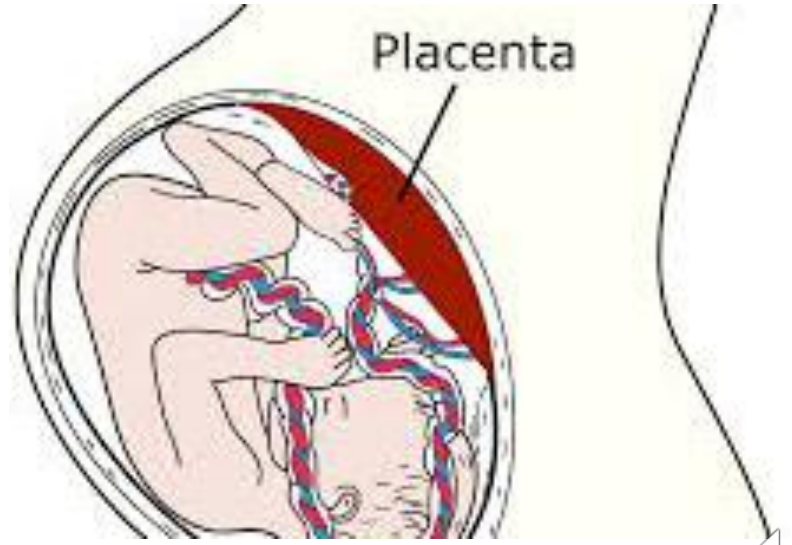
They are small (~40nm diameter), icosahedral, non-enveloped viruses that replicate in the nucleus. Depending on the host cell, they can either transform the cell or replicate the virus and lyze the cell.

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

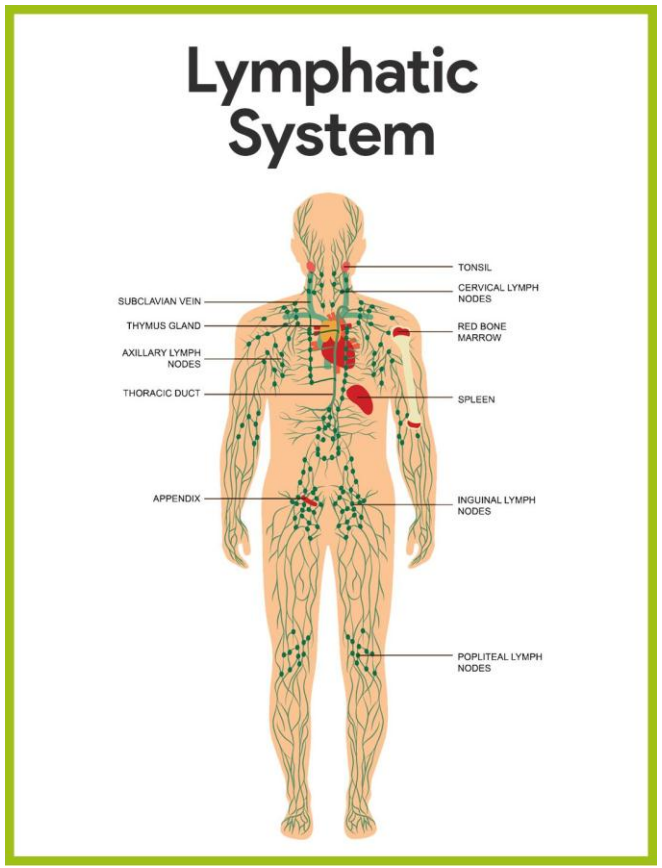
Route of transmission

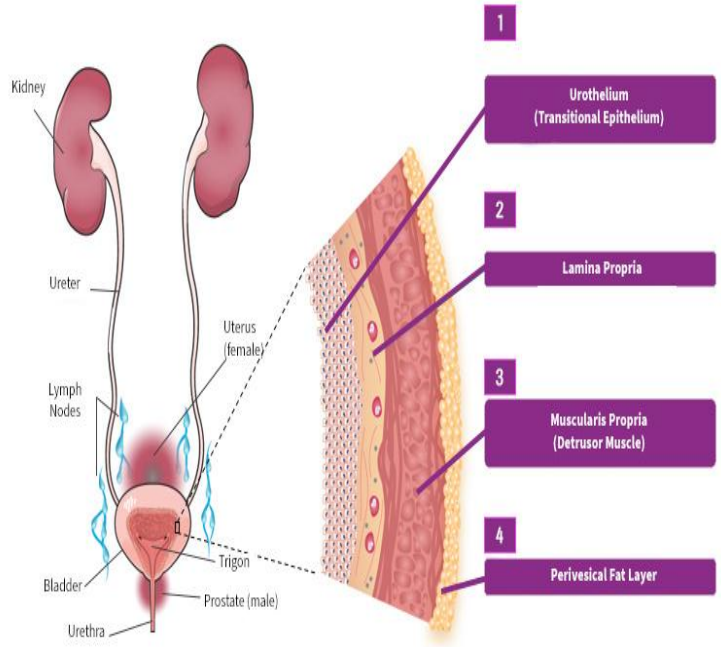




Bohl DL, Brennan DC. BK virus nephropathy and kidney transplantation. Clinical Journal of the American Society of Nephrology. 2007;2(Supplement 1):S36-S46

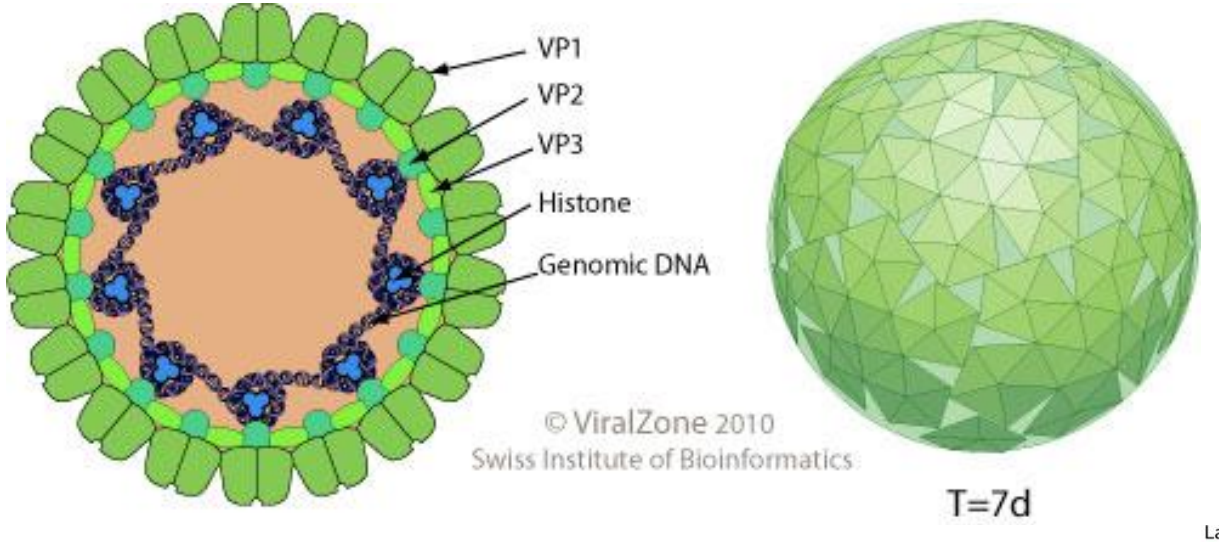
After primary infection, the virus located in the following places and then enter the latent phase.

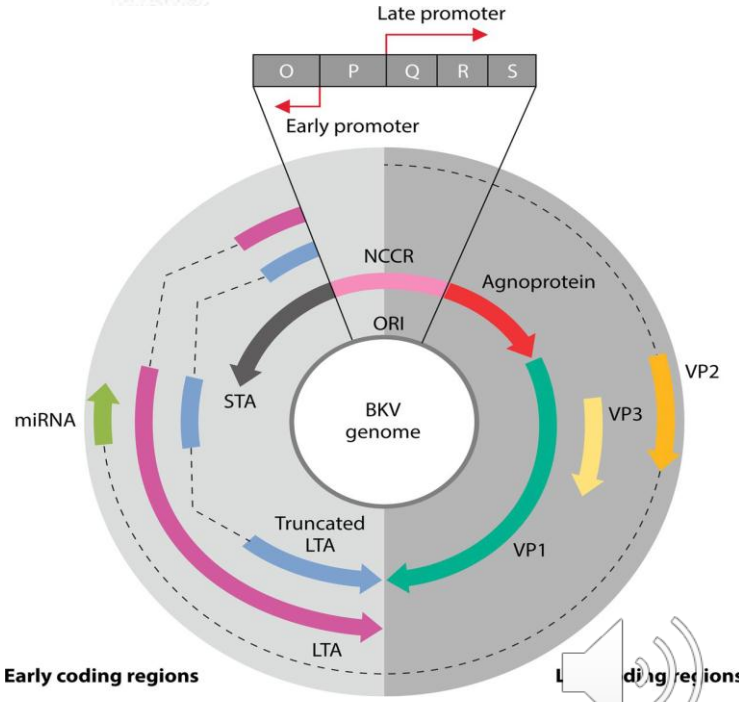




Bohl DL, Brennan DC. BK virus nephropathy and kidney transplantation. Clinical Journal of the American Society of Nephrology. 2007;2(Supplement 1):S36-S46

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.

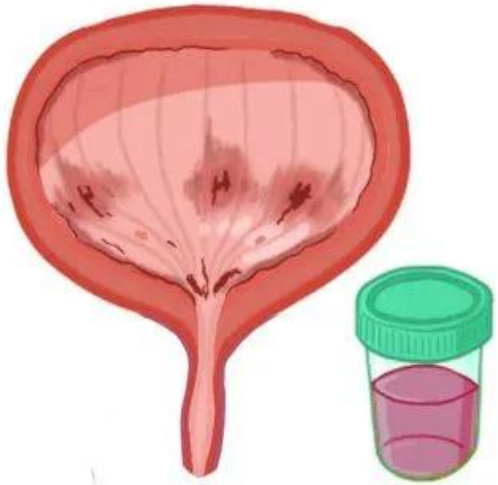




- BK virus infection: an update on diagnosis and treatment
- Deirdre Sawinski and Simin Goral
- Nephrol Dial Transplant (2015) 30: 209–217 doi: 10.1093/ndt/gfu023
- Factors and outcome in BK virus nephropathy in a Hispanic kidney transplant population D. Pe´rez-Torres, J. Bertra´n-Pasarell,E, et al.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

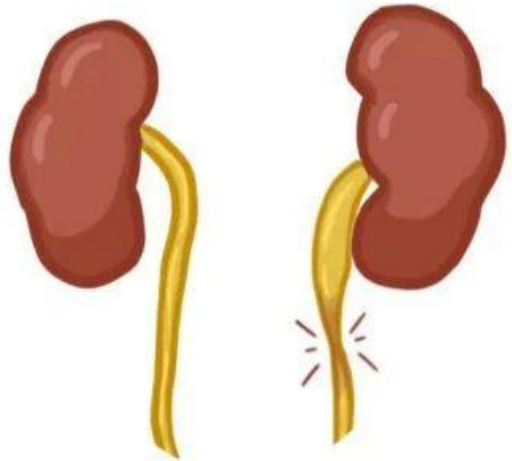
BK VIRUS (BKV)

CLINICAL MANIFESTATIONS

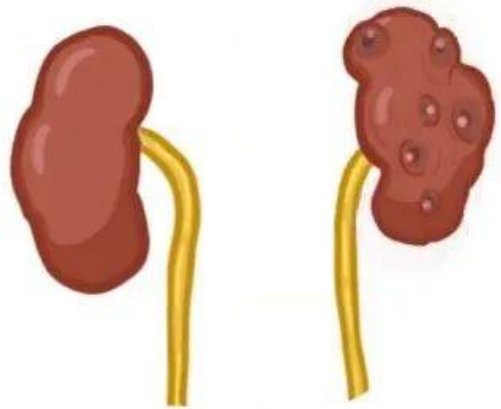


HEMORRHAGIC CYSTITIS

- ↳ BLOODY URINE
- ↳ BONE MARROW TRANSPLANT RECIPIENTS

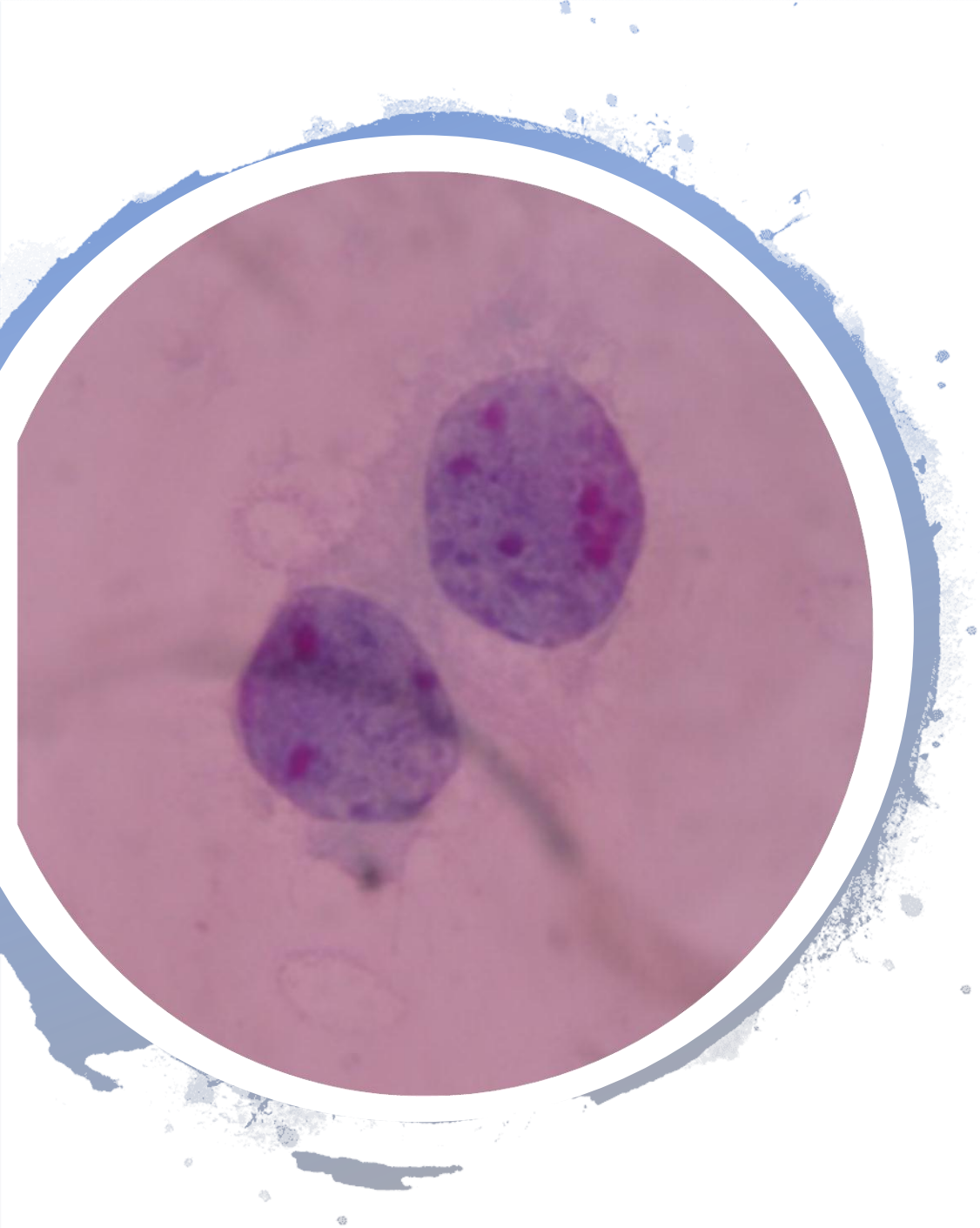


URETERAL STENOSIS



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%.

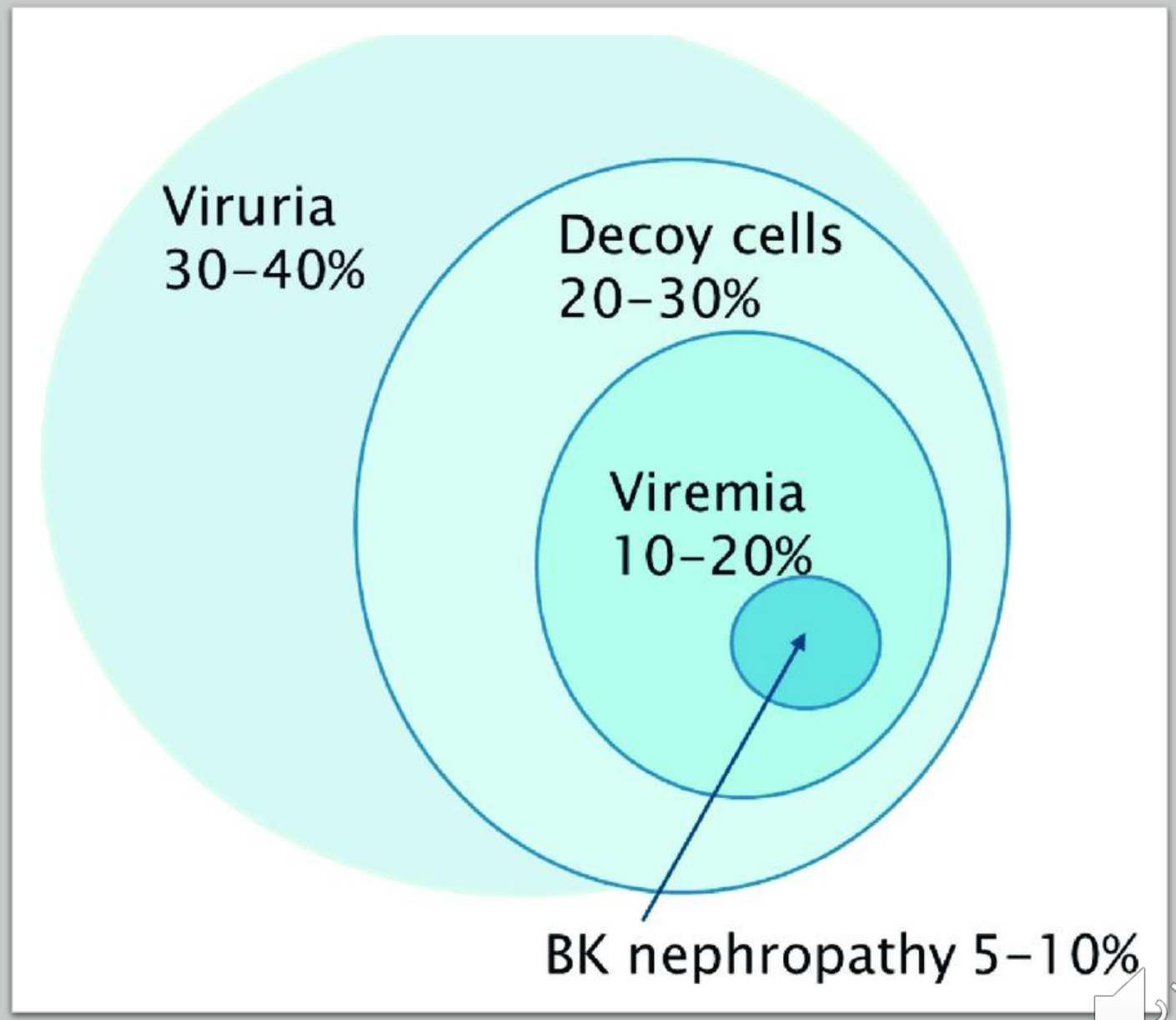
The virus remains latent in urothelium and reactivation (asymptomatic) is often the result of immunosuppression.

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

- 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



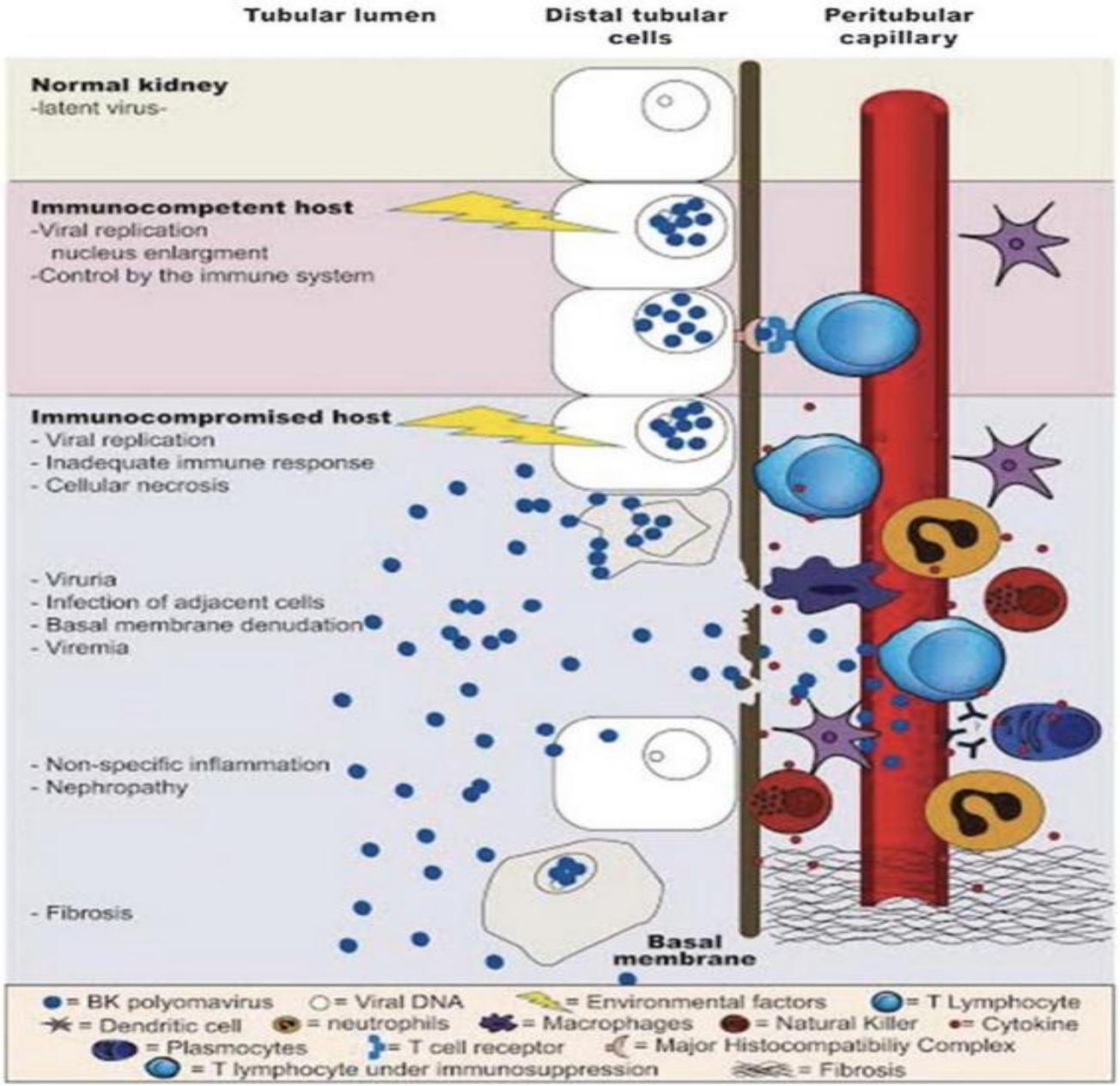


FIGURE 2. Physiopathology of PVAN. Depiction of PVAN development form latency in the uroepithelium (top) to the development of renal inflammation and fibrosis (bottom).

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	• 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.

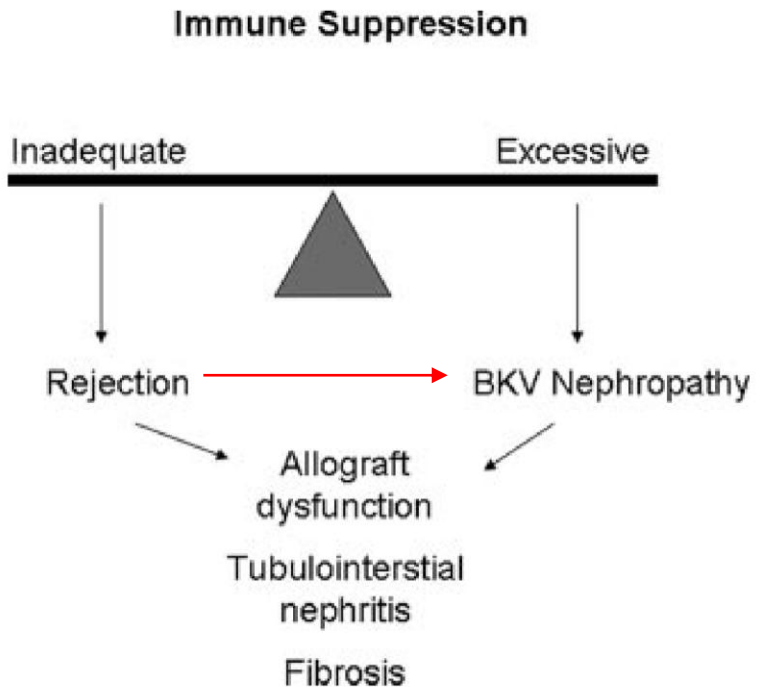


Figure 3. Impaired immune suppression balance. Inadequate immune suppression results in rejection, whereas excessive immune suppression results in BKV nephropathy. Both conditions present as allograft dysfunction with tubulointerstitial nephritis and progression to fibrosis.

- 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

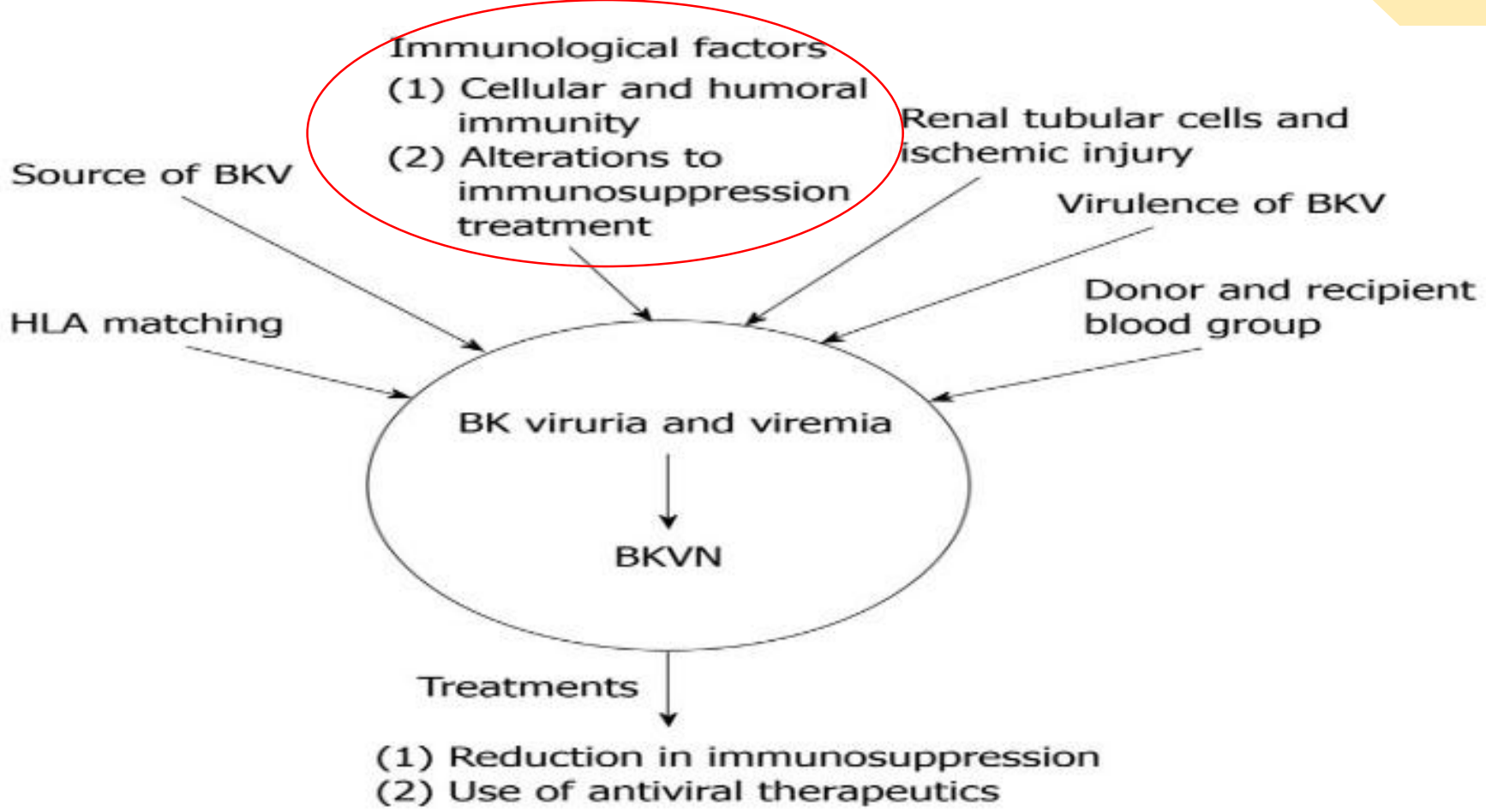


Figure 1 Proposed mechanisms for the pathogenesis of BK virus-associated nephritis after BK virus infection has occurred resulting in BK viruria or BK viremia. These mechanisms include immunological factors, such as alterations to immunosuppressive therapy and cellular and humoral immunity, the source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

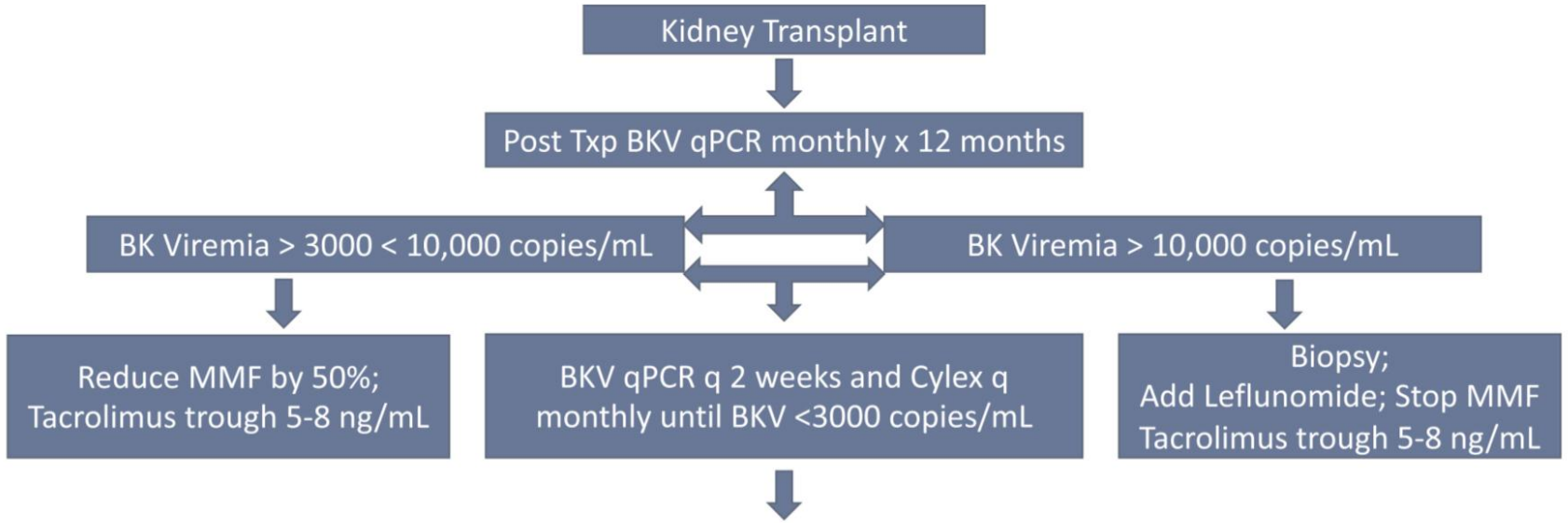
5- JCV may lead to PML, and JCV DNA has been detected in various neoplastic lesions such as oligodendroglioma, astrocytoma medulloblastoma, ependymoma, glioblastoma, colorectal carcinoma, gastrointestinal and bladder cancers.

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



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.

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.

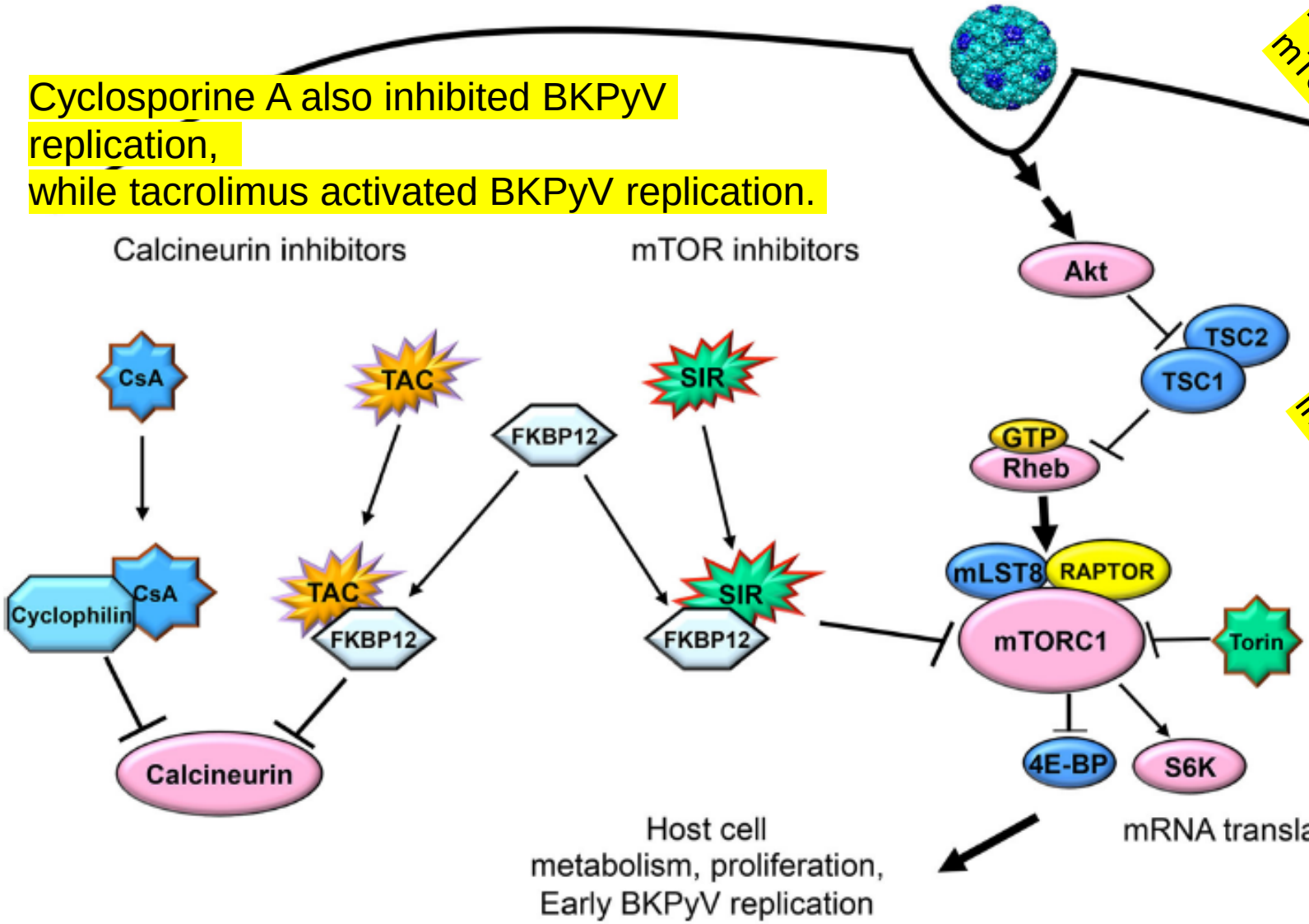


Figure 9: Effects of calcineurin inhibitors and mTOR inhibitors on BKPyV replication. Akt, plasma membrane located, inositol-activated serine-threonine kinase; BKPyV, BK polyomavirus; CsA, cyclosporine A; FKBP, FK binding protein; mTOR, mammalian target of rapamycin; mTORC1, mammalian target of rapamycin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

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

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

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

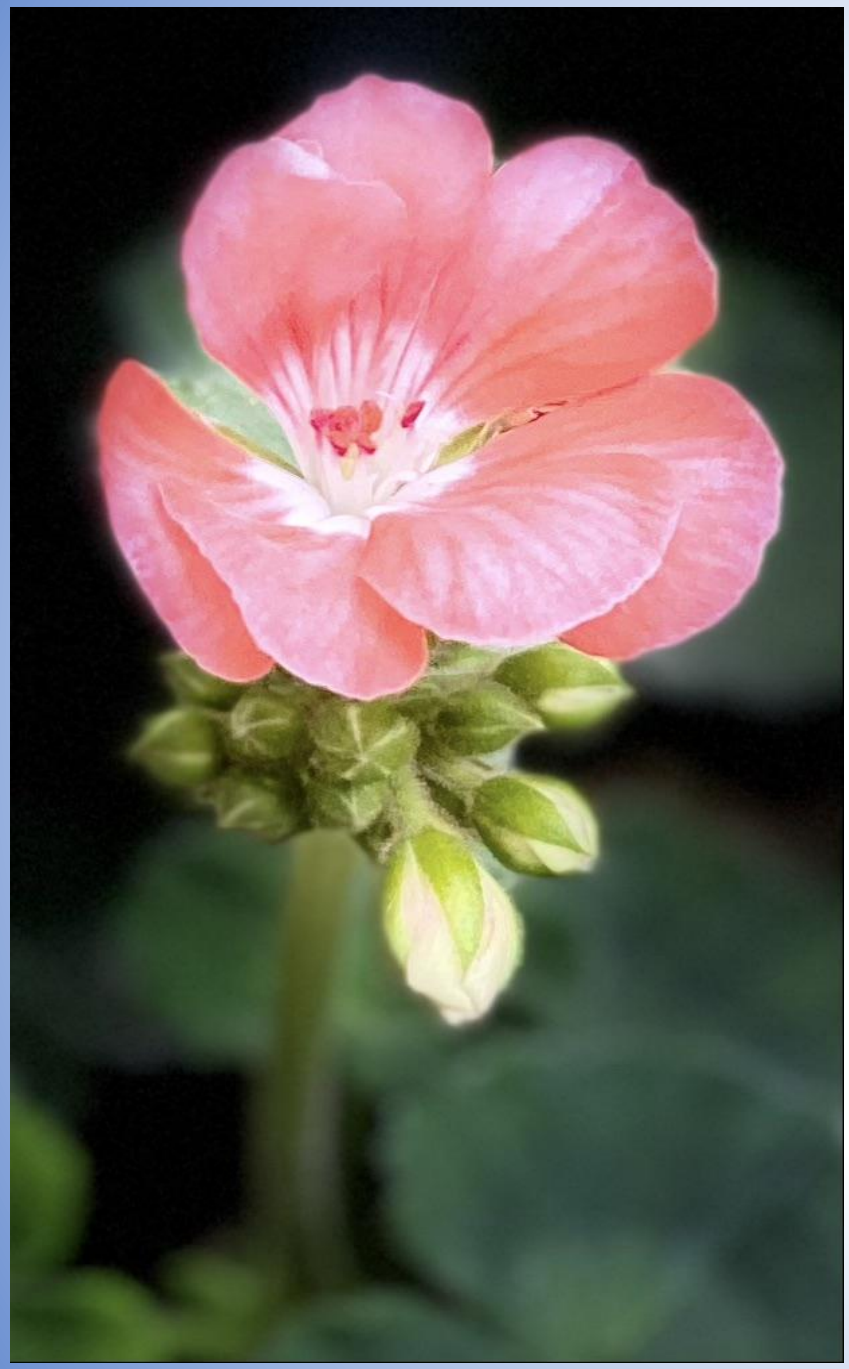
Transpl. Infect. Dis. 2021;23:e13465.

CASE REPORT

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]



They are everywhere, take care.