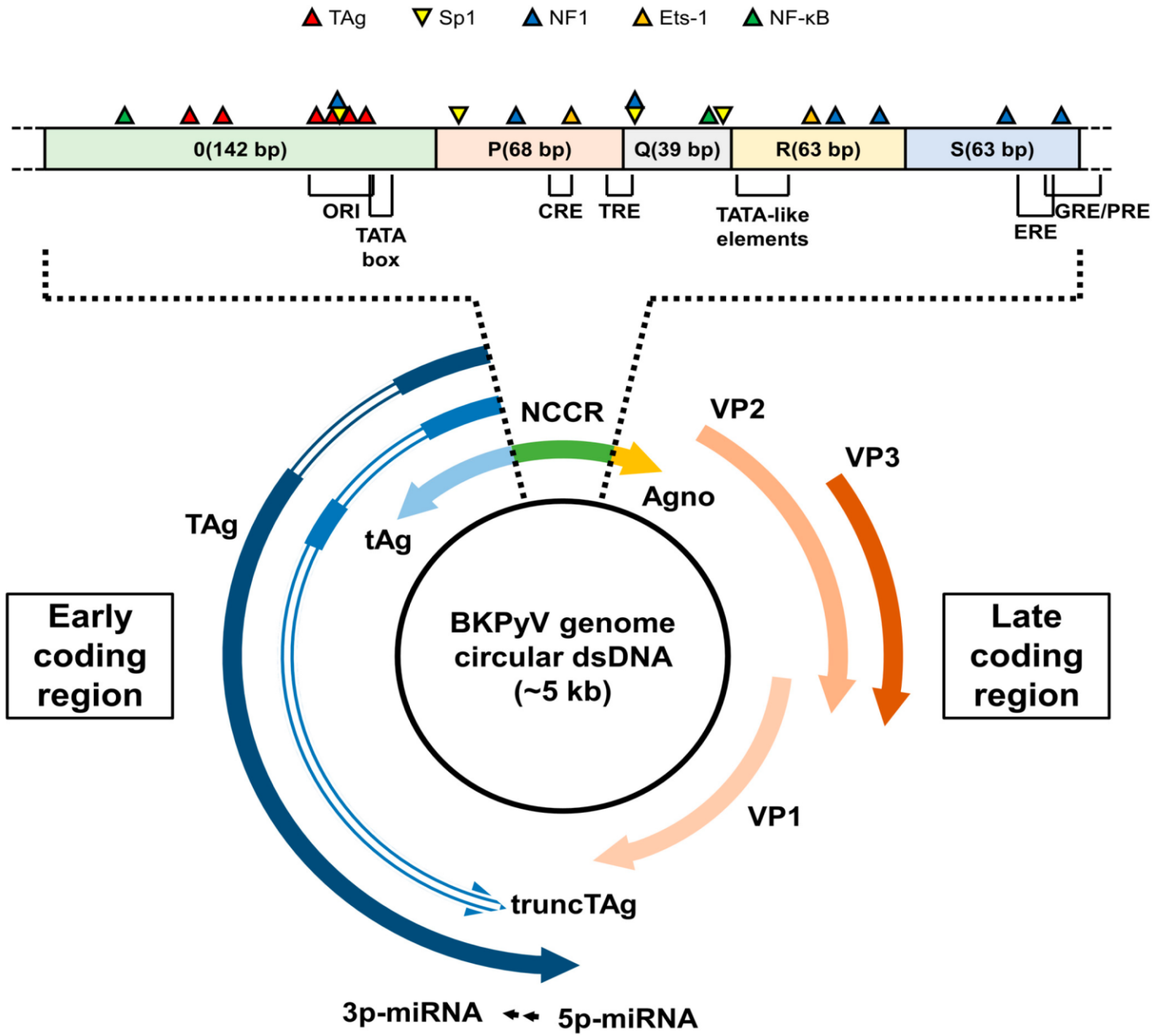
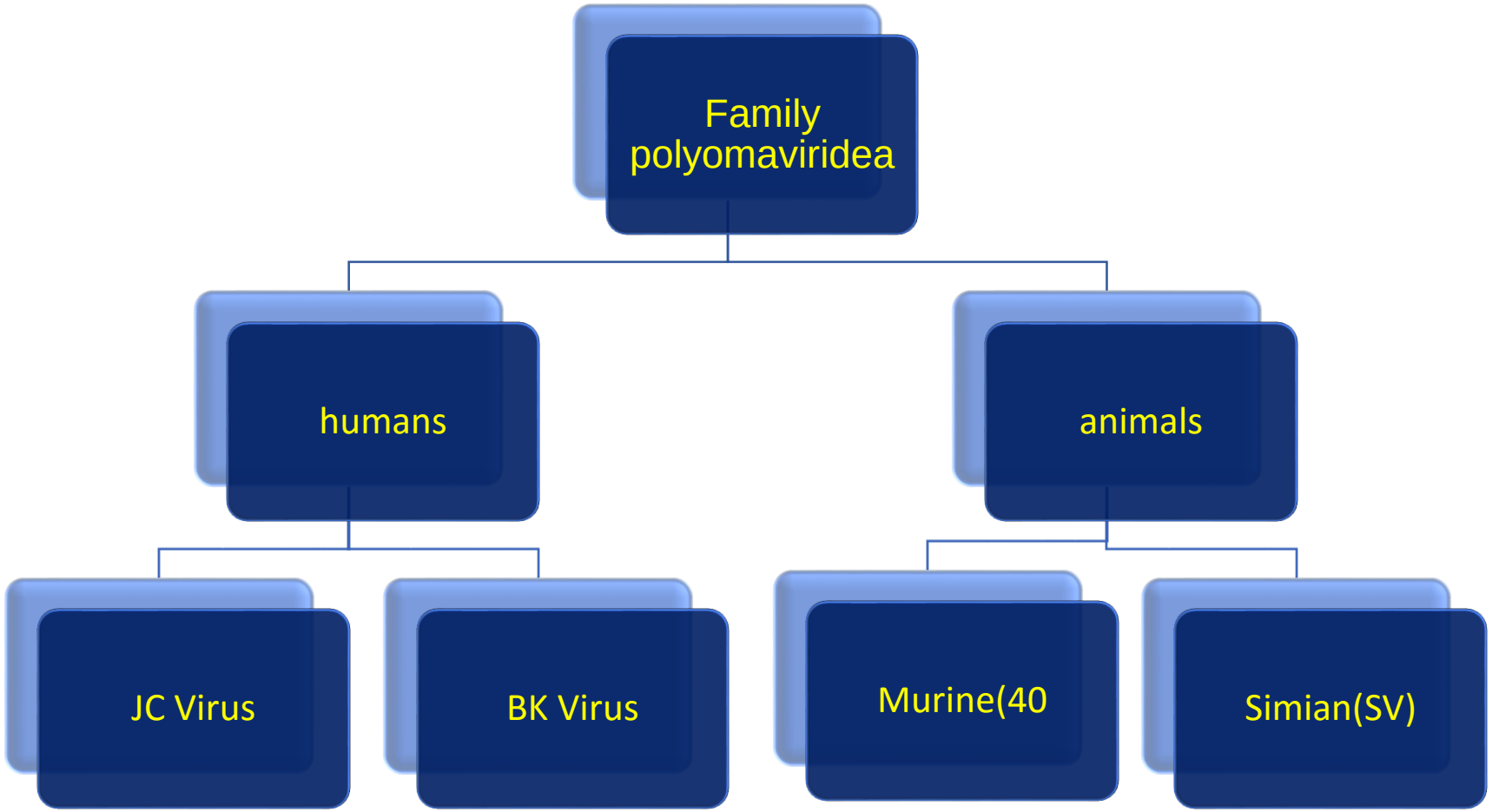
BK Virus Nephropathy Diagnosis & Management Strategies

By Dr.N. Rasaei

Assistant Professor Of Nephrology

SUMS


TAg
Sp1
NF1
Ets-1
NF-κB
0(142 bp)
P(68 bp)
Q(39 bp)
R(63 bp)
S(63 bp)
ORI
TATA box
CRE
TRE
TATA-like elements
ERE
GRE/PRE
NCCR
VP2
VP3
Agno
TAg
tAg
Early coding region
BKPyV genome circular dsDNA (~5 kb)
Late coding region
VP1
truncTAg
3p-miRNA
5p-miRNA


Family polyomaviridea
humans
animals
JC Virus
BK Virus
Murine(40
Simian(SV)

- First reported in a renal transplant patient, BK, in 1971.
- Approx. 80% of the general population has a detectable antibody to BKV, which appears early in life and remains elevated throughout life.
- Primary Infection occurs in early life when it is either asymptomatic or with mild URTI. Thereafter BKV largely persists in the kidneys and urinary tract in a latent form.
- The principal routes of transmission are fecal-oral, respiratory, transplacental, or from donor tissue.

Immunology

- **Cellular**
  - ➢ T cells, especially CD8+, are pivotal to the anti-BK response and surveillance(BK virus specific T cells).

- **Humoral**
  - ➢ BKV-specific antibodies provide incomplete protection against BKVAN for patients after kidney transplantation.
  - ➢ They may attenuate the severity of BKV infection and its clinical manifestations.
  - ➢ Evaluation of BKV-specific antibody titers can provide information on the severity of past or current BKV infections and on prognosis.

(Transplantation 2016;100: 2276–2287)

Risk Factors

Transplant related	Donor related	Recipient related
➉Induction therapy	➉Older age	➉Age (>50)
➉Type & degree of immunosuppression	➉Doner BK Sero-posivity	➉Sex (male)
➉Prior Rx of acute rejection	➉ Degree of HLA matching	➉Race
➉Prolong ischemic time	➉ABO incompatibility	➉Obesity (MBI>30)
➉DGF	➉Donor status(living vs deceased)	➉Previous graft loss due to BK nephropathy
➉Ureteric stent		➉Sero-negativity for BK
		➉CMV
		➉HLA mismatching
		➉High PRA
		➉DM
		➉Dialysis modality before Tx

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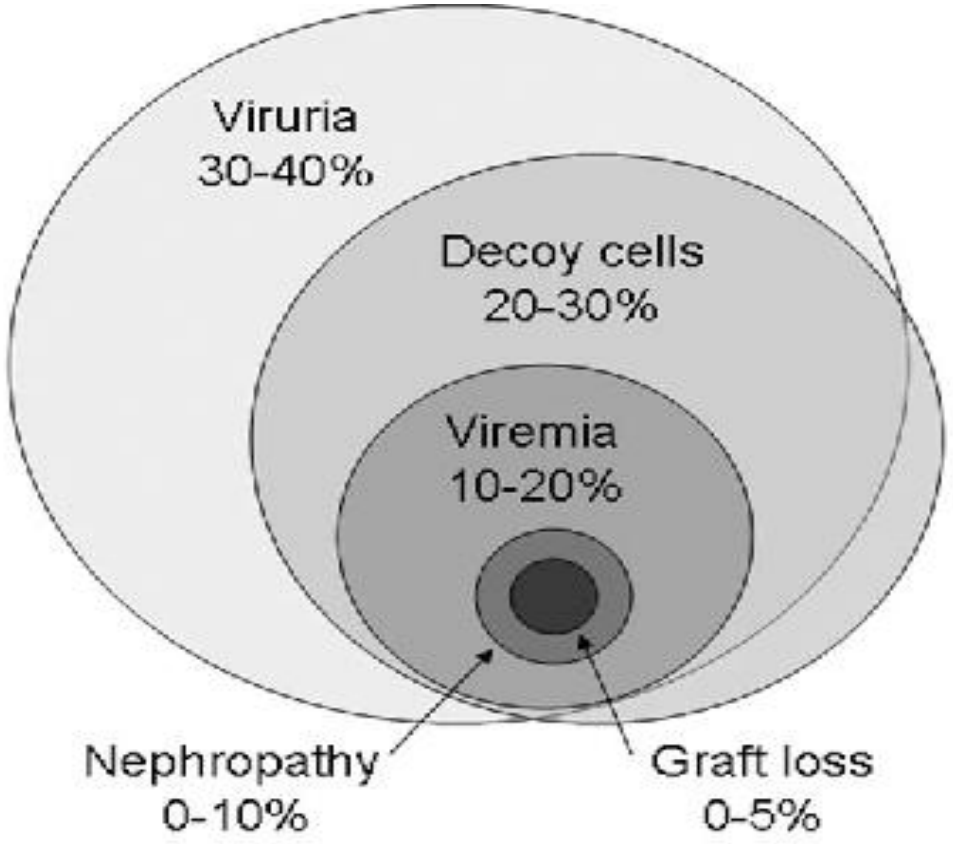
Prevalence of BK Nephropathy In Kidney Transplant Recipients



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

CJASN July 2007, 2 (Supplement 1) S36-S46; DOI: https://doi.org/10.2215/CJN.00920207

Source of BKV Infection

- Two proposed hypotheses:
    1. Transmission occurs through the donor kidney.
    2. Reactivation in the recipient renal epithelium after transplantation

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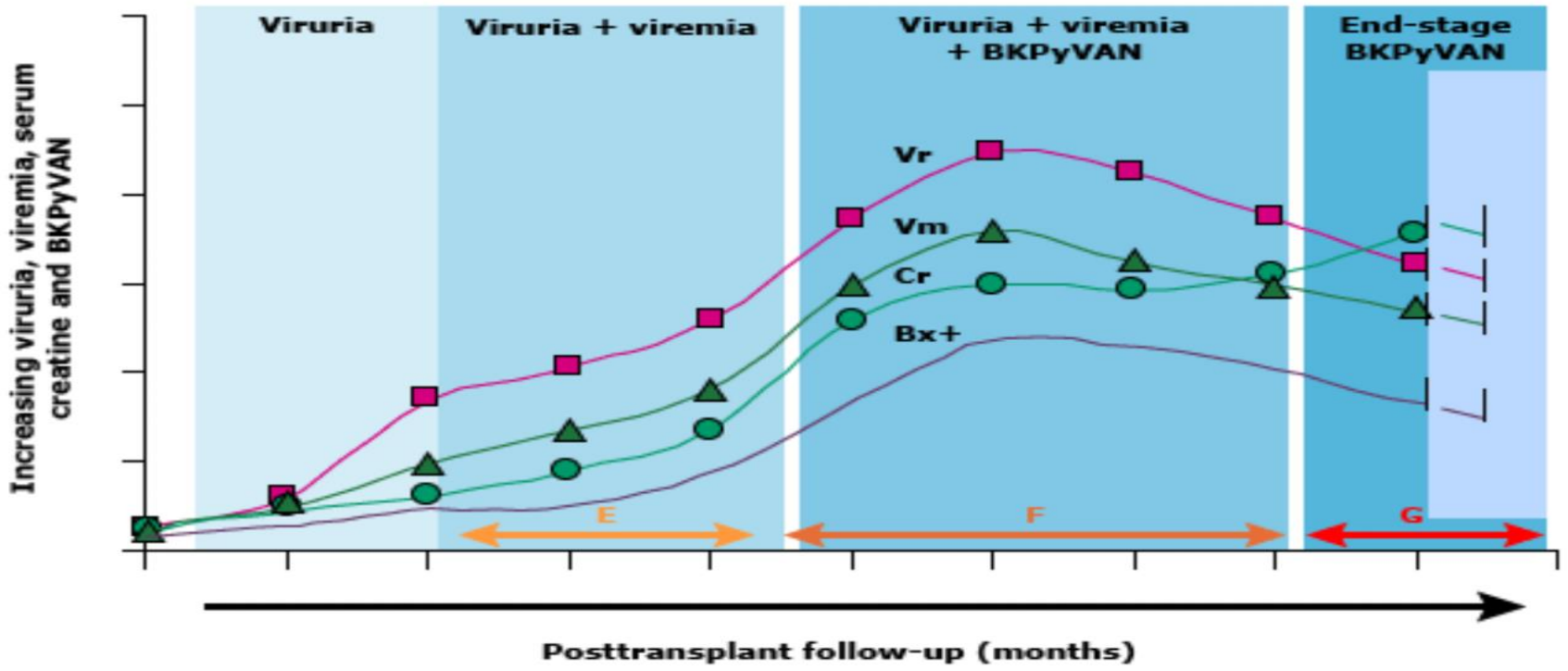
Is Screening Useful?

Clinical Manifestation



Transplantation 2009; 87:621

screening

- **Pretransplant screening of kidney donor and recipient**

  - Donor viuria and genotype
  - donor Vp 1– IgG level
  - recipient Vp 1– IgG level
  - recipient neutralizing IgG
  - recipient viuria and genotype

Not recommended at the present time

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https://doi.org/10.1111/ctr.13528

- **Posttransplant screening of kidney recipients**
  - Plasma quantitative PCR
  - Urine quantitative PCR
  - Urine cytology
  - Renal allograft biopsy
  - new markers

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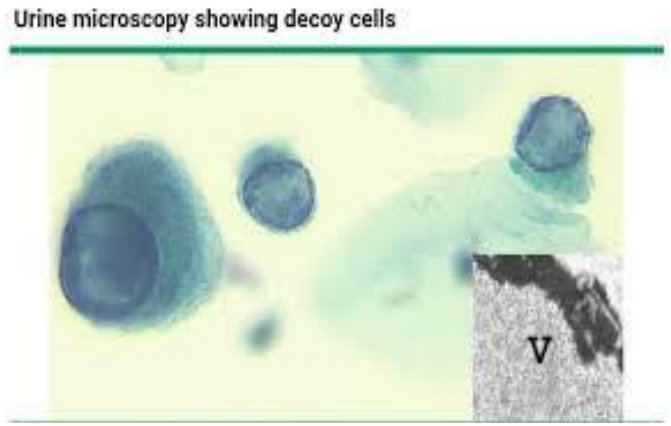
Plasma Quantitative PCR

- Kidney transplant recipients should be screened for BKPyVDNAemia by QNAT to identify patients to be considered for preemptive treatment for PyVAN [strong, moderate].
- Screening for BKPyV-DNAemia permits to identify at least 90% of patients at risk of PyVAN before significant functional impairment of the renal allograft occurs.

Urine Cytology

- Biweekly urine cytology for decoy cells for the first 3 months,
  - ➢then monthly until month 6,
  - ➢then every 3 months until 2 years

posttransplant, and if detectable, followed by testing for BKPyVDNAemia for follow-up and decision making.



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Renal Allograft Biopsy

- A minimum of two biopsy cores should be taken, preferentially containing also medullary tissues [strong, moderate].

PyVAN class-1		PyVAN class-2		PyVAN class-3	
PyVL	Banff *ci* score	*PyVL*	Banff *ci* score	*PyVL*	Banff *ci* score
1	0-1	1	2-3	–	–
–	–	2	0-3	–	–
–	–	3	0-1	3[b]	2-3

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- BKPyV-DNAemia has a positive predictive value of 30%-50% for proven PyVAN with a window period of 2-8 weeks.
- Of note, the false-negative rate of allograft biopsy for PyVAN decreases to <10%:
  - if plasma BKPyV loads increase to more than >6 log10 copies/mL.
  - if renal allograft function has declined from baseline more than 20%.
  - if rearrangements in the BKPyV-NCCR appear in the blood, or if PyV-clusters ("haufen") can be detected by electron microscopy.

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BK Nephropathy VS Rejection

- Tubulitis is not a reliable discriminating parameter.
- Immunohistochemistry and electron microscopy in more advanced PyVAN can respectively highlight C4d and immune complex deposits in the tubular basement membranes but not in peritubular capillaries.
- Endarteritis usually reflects antibody- or T-cell mediated injury and is associated with poor outcome.

Micro-RNA

- Detection of BKPyV microRNA in body fluids including urine and blood has been explored for diagnostic purposes, but the higher specificity for disease needs to be balanced against the lower sensitivity of miRNA quantification/levels compared to standard BKPyV-DNA quantification.
- BKPyV VP1-mRNA in urine, with the potential advantage of interrogating other transcript marker combinations of immune activation and rejection or BKPyV-DNAemia.

J Clin Virol. 2018;102:70-76.

Method	Sensitivity* (%)	Specificity* (%)	PPV*	NPV*	Advantage	Disadvantage
Plasma quantitative PCR[¶] (preferred)	100	88[Δ]	Moderate	High	▪ High PPV for BKPyVAN if VL ≥ 10,000/mL plasma ▪ Ability to monitor response to therapy (ie, reduction in immunosuppression)	▪ Relatively expensive ▪ Nonstandardized significant variability among assays ▪ Rare reports of biopsy-confirmed BKPyVAN without concomitant viremia/DNAemia
Urine quantitative PCR	100	78	Moderate	High	▪ Precedes BKPyV viremia by 6 to 12 weeks ▪ Earlier identification of patients at risk for subsequent BKPyVAN	▪ Limited utility for monitoring response to therapy (ie, immunosuppression reduction) ▪ May remain persistently positive
Urine decoy cells	100	71	Low	High	▪ Lower cost	▪ Decoy cells identification needs experience ▪ Does not distinguish among polyomaviruses (ie, JCPyV versus BKPyV)
Urine Haufen	100	99	High	High	▪ High PPV ▪ Might be useful in settings where allograft biopsy is not feasible	▪ Requires electron microscopy ▪ Not widely available

1. *N Engl J Med 2002; 347:488. 2. J Am Soc Nephrol 2009;*
3. *Am J Clin Pathol 2010; 133:242 20:416*

Specimen	Marker (test, *comments*)	Clinical diagnosis of PyVAN			
		Possible	Probable	Presumptive	Proven
Urine	"High-level viruria"	+	+	+	+
	Decoy cells *(check if inflammation and/or casts)*				
	BKPyV urine DNA load > 7 $\log_{10}$ copies/mL				
	BKPyV *VP1* mRNA load > 6.5 $\log_{10}$ copies/ngRNA				
	PyV particles *(check if in clusters or "haufen")*				
Plasma	"BKPyV-DNAemia"	–	+	+	+
	Plasma load > 3 $\log_{10}$ copies/mL (*sustained in 2 measurements in < 3 weeks*)		+		
	Plasma load > 4 $\log_{10}$ copies/mL (*increased in 1 of 2 measurements in <3 weeks*)			+	
Biopsy	Polyomavirus-associated nephropathy	–	–	–	+
	Viral cytopathic changes				[a]
	Inflammatory infiltrates/tubulitis				[a]
	More than mild interstitial fibrosis/tubular atrophy				[a]
Treatment	Recommendation[b]	No	(Yes)	Yes	Yes

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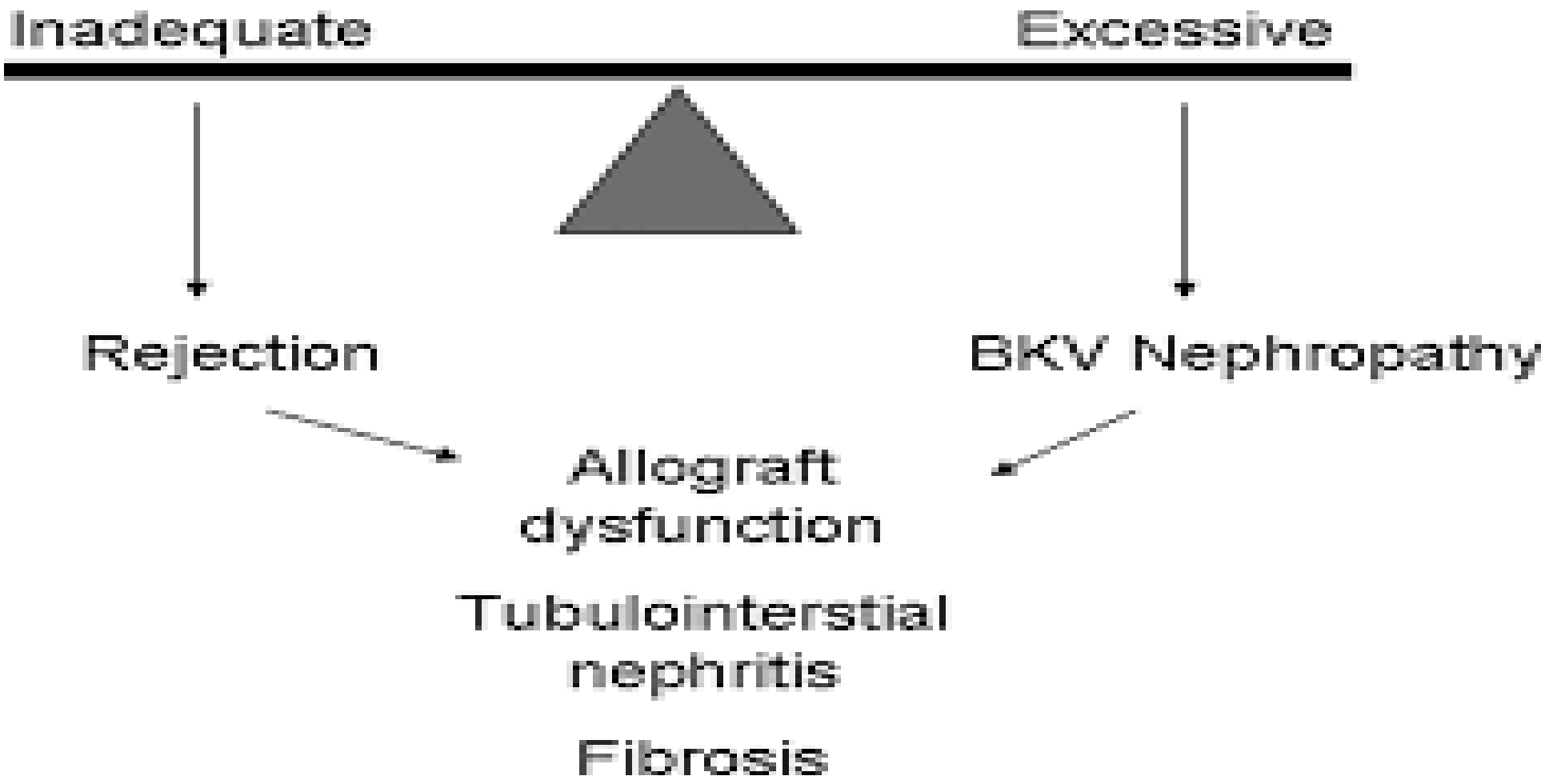
Treatment

Immune Suppression



CJASN July 2007, 2 (Supplement 1) S36-S46; DOI: https://doi.org/10.2215/CJN.00920207

Treatment Of BKPyV-DNAemia And PyVAN In Kidney Transplant Recipients

- The following strategies and their combinations have been reported:
  - Strategy 1.
    - First dose reduction in the calcineurin inhibitor by 25%-50% in one or two steps, followed by reducing the antiproliferative drug by 50%.
  - Strategy 2.
    - First reducing the antiproliferative drug by 50% followed by reducing calcineurin inhibitors by 25%-50% followed by discontinuing the antiproliferative drug.
- Oral prednisone is typically tapered to 10 mg or less per day.

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https://doi.org/10.1111/ctr.13528

Strategy 1

- First decrease the dose of the calcineurin inhibitor by 25 to 50 percent in one or two steps
- Followed by reducing the antimetabolite by 50 percent
- Followed by discontinuing the antimetabolite.

Strategy 2

- In patients who are on a triple immunosuppression therapy :
  - Initially reduce the dose of the antimetabolite by 50 percent.
  - If the BKPyV viral load does not decrease within two to four weeks, completely discontinue the antimetabolite.
  - If there is still no decrease in viral load after another two weeks, decrease the dose of the calcineurin inhibitor by 25 to 50 percent.

- Tacrolimus trough levels are commonly targeted to <6 ng/mL [strong, moderate].
- Cyclosporine trough levels to <150 ng/mL [strong, moderate].
- Sirolimus trough levels of <6 ng/mL [weak, very low].
- More advanced disease, targeting trough levels for tacrolimus of <3 ng/mL and cyclosporine of <100 ng/mL.

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- In cases with sustained BKPyV-DNAemia and biopsy-proven acute rejection (with or without evidence of concurrent PyVAN), antirejection treatment has priority, and in case of clinical and laboratory response be followed by reducing immunosuppression in a second step (eg, after 2 weeks).

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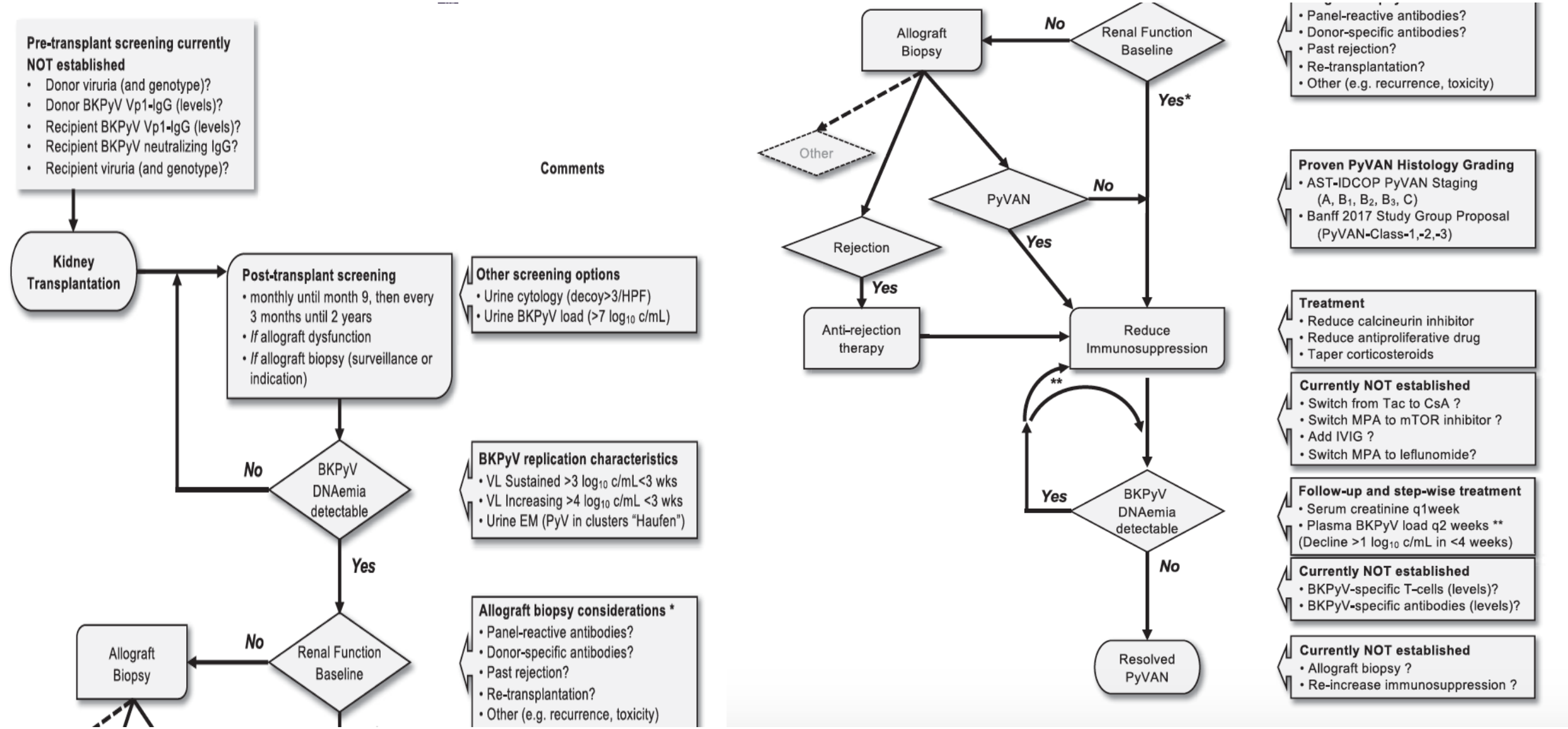

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Adjuvant Therapy

- Intravenous immunoglobulin (IVIG)
- Leflunomide
- Fluoroquinolones
- Cidofovir
- Conversion of tacrolimus to cyclosporine
- Conversion to m-TORi
- Cell-based therapies

Intravenous Immunoglobulin (IVIG)

- preparations have been administered in doses ranging from 0.1 to 2.0 g/kg in conjunction with reduced immunosuppression.
- Available IVIG preparations contain high titers of potent BKPyV neutralizing antibodies.
- Although IVIG does not penetrate the intracellular compartment, its direct neutralizing activity and plethora of indirect immunomodulatory effects could contribute to an improved resolution of active disease.

Clinical Transplantation. 2019;33:e13528.
https://doi.org/10.1111/ctr.13528

- IVIG is administered at a dose of 300 mg/kg every three weeks in conjunction with a reduction in immunosuppression.
- The adjunctive use of IVIG may be considered in patients:
  - with established BKPyVAN who do not respond to a reduction in immunosuppression and who also have severe hypogammaglobulinemia ([IgG] <400 mg/dL).

Efficacy of Intravenous Immunoglobulin in the Treatment of Persistent BK Viremia and BK Virus Nephropathy in Renal Transplant Recipients

D. Vu[a,b,c,d,e], T. Shah[c,d,e,f], J. Ansari[d], R. Naraghi[d,e], and D. Min[c,e,*]

[a]American University of Health Sciences, Signal Hill, California, United States; [b]National Institute of Transplantation, Los Angeles, California, United States; [c]Western University of Health Sciences, Pomona, California, United States; [d]Transplant Research Institute, Los Angeles, California, United States; [e]St.Vincent Medical Center, Los Angeles, California, United States; and [f]University of Southern California, Los Angeles, California, United States

IVIG administration appeared to be safe and effective in treating BKV viremia and BKVN and preventing graft loss in patients who had inadequate response to immunosuppression reduction and leflunomide therapy.

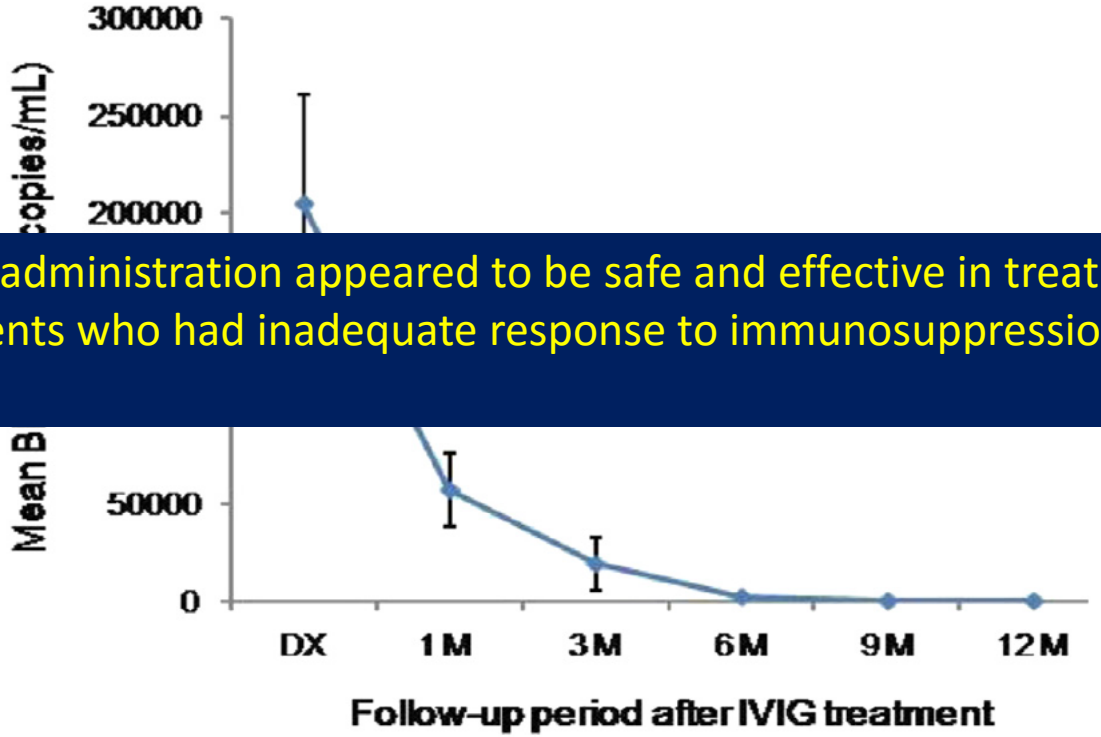


Fig 1. Mean plasma BKV DNA measured using quantitative real-time PCR assay at the time of IVIG administration (Dx) and at 1, 3, 6, 9, and 12 months after IVIG therapy.

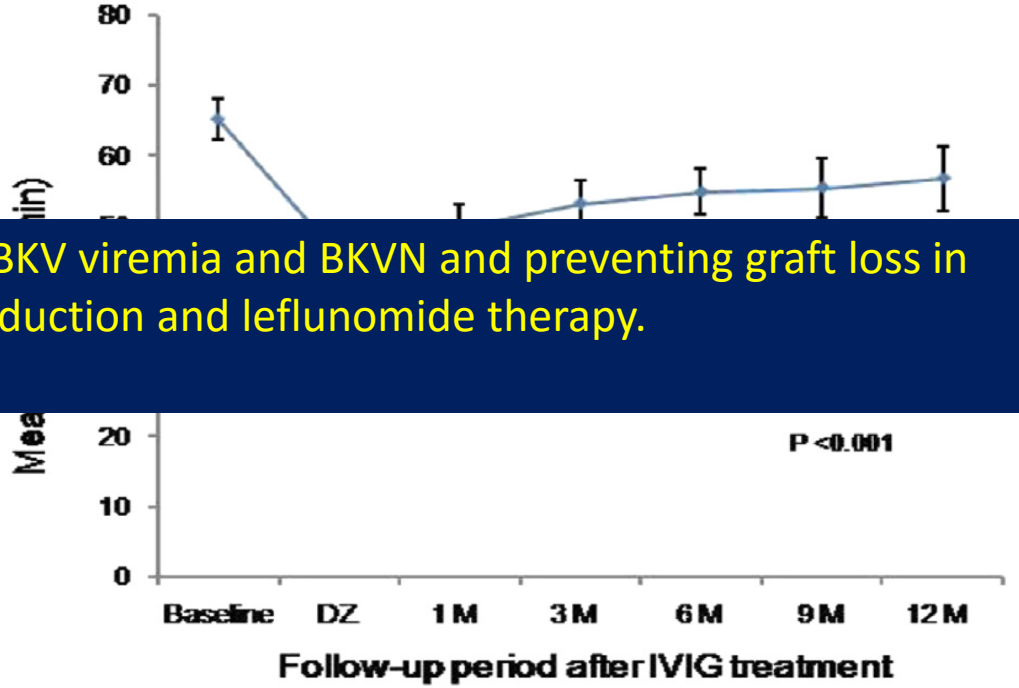


Fig 2. Mean GFR (mL/min) levels in kidney transplant recipients with BKVN. Levels were taken from patients before (baseline), at the time of IVIG administration, and at 1, 3, 6, 9, and 12 months after IVIG therapy.

Intravenous Immunoglobulin as a Treatment for BK Virus Associated Nephropathy: One-Year Follow-Up of Renal Allograft Recipients

Alp Sener,[1] Andrew A. House,[2] Anthony M. Jevnikar,[2] Neil Boudville,[2] Vivian C. McAlister,[3] Norman Muirhead,[2] Faisal Rehman,[2] and Patrick P. W. Luke[1,4]

BK virus associated nephropathy (BKVAN) has emerged as an important cause of renal allograft dysfunction and graft loss. Although several treatment strategies have been proposed, the rate of graft loss remains high. We studied the outcome of renal transplant patients with BKVAN treated with IVIG. After 11.4±3.9 months (mean±SEM) from the time of transplantation, 8 renal allograft recipients were diagnosed with BKVAN. In addition to a reduction of immunosuppressive therapy, patients received 2 g/kg IVIG. After a mean follow-up of 15 months, all except one patient are currently off dialysis. In summary, after IVIG therapy, 88% of patients still have functioning grafts, although renal function continues to be impaired. The benefit of concomitant IVIG and reduction of immunosuppressive therapy in BKVAN needs to be further addressed in randomized, multicentered trials.

Keywords: Renal allograft, BK virus, Immunoglobulin, Nephropathy.

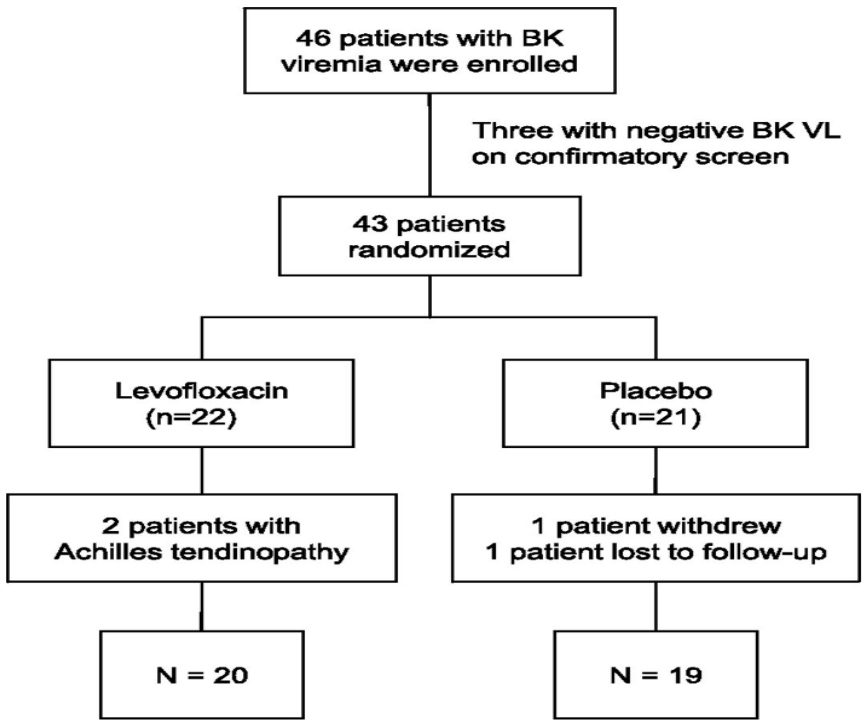
(*Transplantation* 2006;81: 117–120)

Efficacy of Levofloxacin in the Treatment of BK Viremia: A Multicenter, Double-Blinded, Randomized, Placebo-Controlled Trial

Belinda T. Lee, Steven Gabardi, Monica Grafals, R. Michael Hofmann, Enver Akalin, Aws Aljanabi, Didier A. Mandelbrot, Deborah B. Adey, Eliot Heher, Pang-Yen Fan, Sarah Conte, Christine Dyer-Ward and Anil Chandraker

CJASN March 2014, 9 (3) 583-589; DOI: https://doi.org/10.2215/CJN.04230413

Study design.



Belinda T. Lee et al. CJASN 2014;9:583-589

Outcome	Levofloxacin Group (*n*=20)	Placebo Group(*n*=19)	*P* Value
Reduction in BK viral load at 3 mo (%)	70.3±42.5	69.1±39.5	0.93
Patients with >50% reduction in BK viral load at 3 mo	15 (75)	13 (68)	0.73
Reduction in BK viral load at 6 mo (%)	82.1±34.7	90.5±22.2	0.38
Patients with >50% reduction in BK viral load at 6 mo	16 (84) (*n*=19)	17 (89) (*n*=19)	>0.99
Increase in BK viral load at 3 mo	5 (25)	3 (16)	0.69
Sustained BK viremia at 3 m			
Sustained BK viremia at 6 m			
Allograft loss			

Conclusions A 30-day course of levofloxacin does not significantly improve BK viral load reduction or allograft function when used in addition to overall reduction of immunosuppression

tart of study

Study Time Point	Levofloxacin Group	Placebo Group	*P* Value
BK viremia diagnosis	1.6±0.4	1.8±0.8	0.19
1 mo	1.6±0.5	1.9±0.9	0.32
2 mo	1.6±0.5	1.6±0.6	0.76
3 mo	1.5±0.4	1.8±0.9	0.21
6 mo	1.5±0.5	2.1±1.6	0.17

Clin J Am Soc Nephrol 9: 583–589, 2014. doi: 10.2215/CJN.04230413

Conversion Of Tacrolimus To Cyclosporine

- Cyclosporine was found to suppress primary BKVinfection in vitro, and this effect was shown to be dose-independent and not related to cytotoxicity.
- cyclosporine in these experiments did not have any influence on the cells with high-level infection (>109copies/mL).

Cell-based Therapies

European Journal of Haematology

CASE REPORT

BKV-specific T cells in the treatment of severe refractory haemorrhagic cystitis after HLA-haploidentical haematopoietic cell transplantation

Oscar M. Pello, Andrew J. Innes, Anne Bradshaw, Sally-Anne Finn, Shab Uddin ... See all authors

First published: 13 January 2017 | https://doi.org/10.1111/ejh.12848 | Citations: 27

Case report

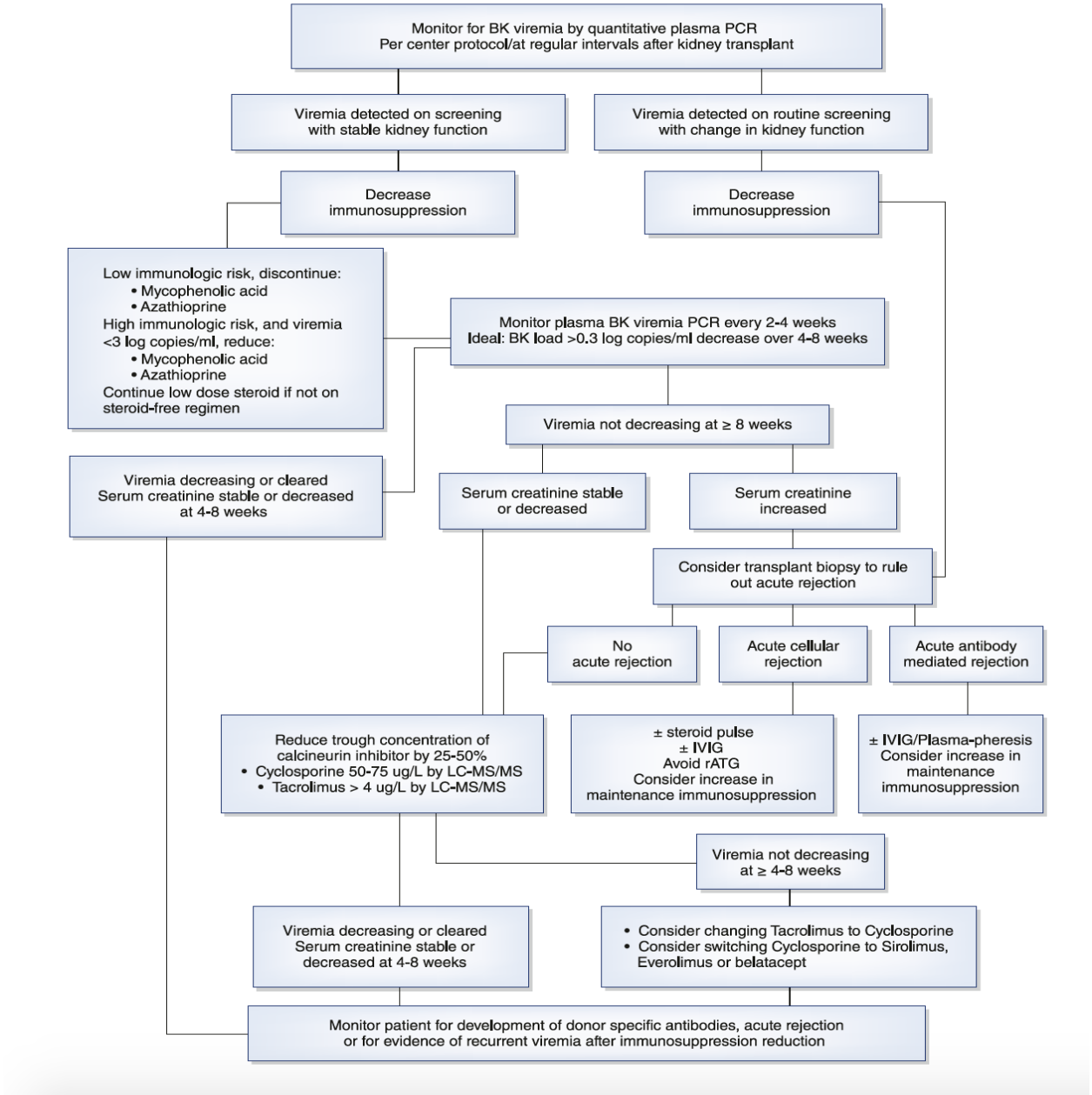
Here, we present a patient who, following haploidentical HCT, developed severe BKV haemorrhagic cystitis, resistant to standard therapy. He responded well to adoptive transfer of donor cells enriched in BKV-specific T cells using the new second-generation CliniMACS Prodigy and the Cytokine Capture System from Miltenyi Biotec. Treatment led to full resolution of both the symptoms and viraemia without unwanted complications.

Conclusion

Our observations suggest that use of products enriched with BKV-specific T cells generated using this system is safe and efficient in HLA-haploidentical HCT where BKV cystitis can be a serious complication.

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.

Proposed algorithm for the management of kidney transplant recipientswith BK Viremia or BK nephropathy



Clin J Am Soc Nephrol 13: 1893–1896, December, 2018

Retransplantation After Allograft Failure Following PyVAN

- Surgical removal of the primary transplant has been performed in approximately half of all cases but did not protect against recurrent BKPyV replication and PyVAN.
- In case of retransplantation of patients with persistent BKPyV-DNAemia, a significant decline of at least 2 log10 copies/mL indicative of emerging BKPyV-specific immune control should be achieved and prior graft nephrectomy considered.

Clinical Transplantation. 2019;33:e13528.
https://doi.org/10.1111/ctr.13528

- There are no data regarding the necessity of bilateral surgical removal of the native kidneys, which may serve as a reservoir and source of reinfection, particularly in cases of neo-ureteral stent placement.
- Induction therapy is not contraindicated after clearance of BKPyV-DNAemia but extended periods of intense maintenance immunosuppression should be avoided.

Clinical Transplantation. 2019;33:e13528.
https://doi.org/10.1111/ctr.13528

Conclusions

- The infection can cause significant deleterious effects, such as BKV nephropathy in kidney transplant recipients.
- Screening protocols have been implemented to detect the infection early after transplant.
- The most commonly used method is the detection of viral replication in blood with polymerase chain reaction testing.
- There are no specific antiviral agents.
- The mainstay of treatment is IS reduction while, at the same time, preventing rejection episodes.

Nephrol Dial Transplant (2019) 1–3doi: 10.1093/ndt/gfz214
Transplant Research and Risk Management 2019:11


بیمارستان موقوفه محمد نمازی