BK Virus Nephropathy

Prevalence & Impact

Dr. Fatemeh Yssari

Nephrologist

SBMU

1400

BK VIRUS

- viral infections after renal transplantation have emerged as an important cause of allograft loss.
- BK is a common posttransplant opportunistic viral infection, affecting ~15% of renal transplant recipients in the first posttransplant year.

VIROLOGY

- The polyomaviruses are small (30 to 45 nm), icosahedral, nonenveloped, double-stranded, closed circular DNA virus that are ubiquitous to humans, occurring with a seroprevalence of up to 80 percent.

VIROLOGY

- The 5 kb genome encodes six viral proteins. There are two "early" nonstructural or enzymatic proteins, an agnoprotein, and three "late" proteins. The early proteins are the large tumor antigen, or "T antigen," and the small tumor antigen, or the "t antigen.
- " The T antigen is responsible for cell immortalization and the establishment of latent infection. The agnogene, appears to aid in the assembly of viral particles.
- The "late" genes encode three viral capsid proteins, VP-1, VP-2, and VP-3, which mediate cell entry and progeny virion assembly.

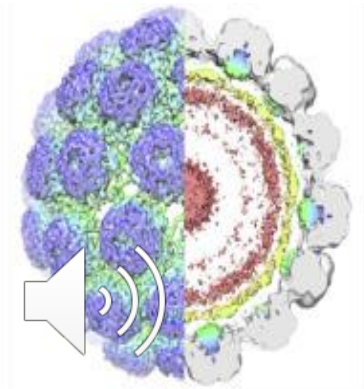
Review

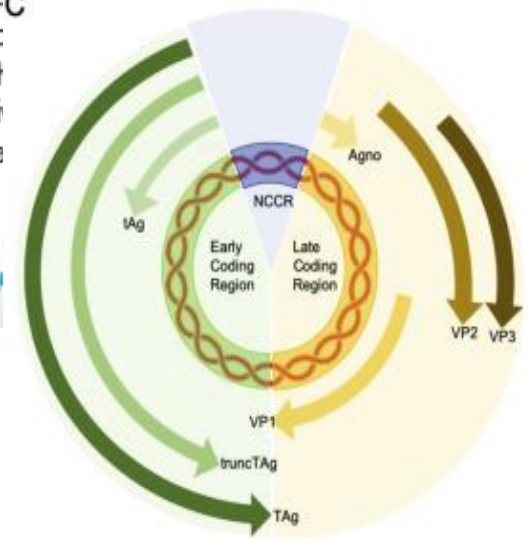
Kidney Medicine

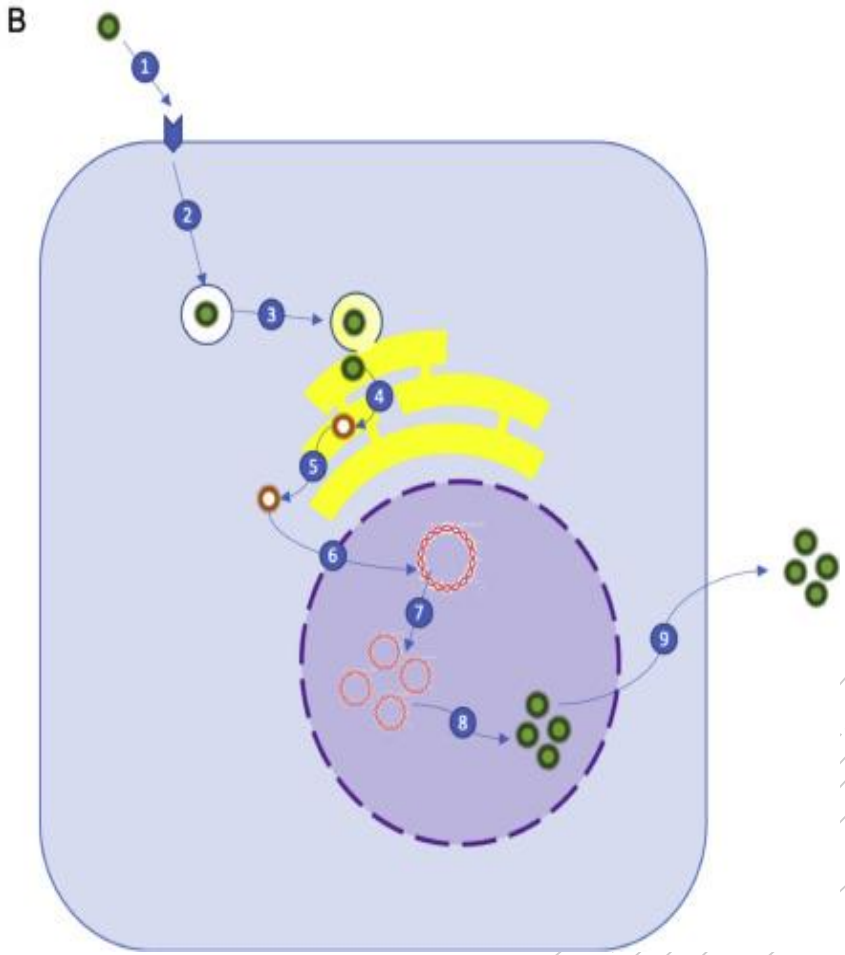
Advances in BK Virus Complications in Organ Transplantation and Beyond

Abraham Cohen-Bucay, Silvia E. Ramirez-Andrade, Craig E. Gordon, JA
Vipul C. Chitalia

Reactivation of BK virus (BKV) remains a dreaded complication in immunos
tionally, BKV is known as a cause for BKV-associated nephropathy and all
transplant recipients. However, emerging studies have shown its negativ
function and patient survival in other transplants and its potential role in
Because BKV-associated nephropathy is driven by immunosuppression,
convenient standard of care. However, this strategy is risk prone due to the de
antibodies affecting long-term allograft survival. Despite its pathogenic role
effective anti-BKV therapeutics. This limitation combined with increased morb
BKV-associated diseases add to the complexity of BKV management. Wh
vances in the pathogenesis of BKV-associated nephropathy and its reacti
plants, this review illustrates the limitations of current and emerging therape
compelling argument for an effective targeted anti-BKV drug.

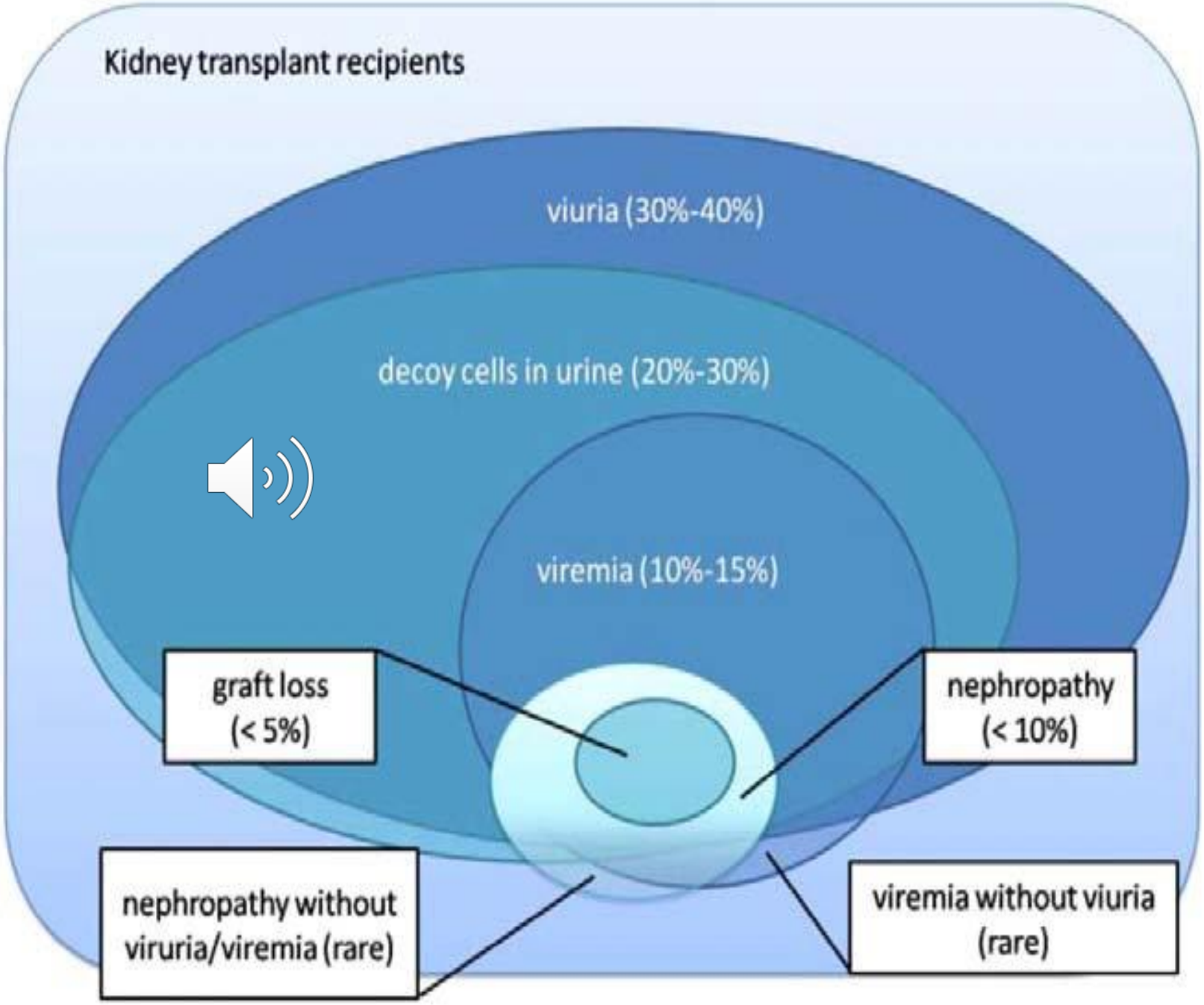






BK Virus Nephropathy

Prevalence



International Journal of Nephrology and Renovascular Disease Dovepress

REVIEW

BK Virus Nephropathy: Prevalence, Impact and Management Strategies

This article was published in the following Dove Press journal:
International Journal of Nephrology and Renovascular Disease

Rajeev Sharma[1,2]
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Abstract: BK virus reactivation as a result of therapeutic immunosuppression following renal transplant can result in BK polyomavirus nephropathy and renal allograft loss. This is a complex and challenging clinical problem with a range of management options and practices reported in literature. The current standard for early diagnosis and treatment is surveillance by measuring viral DNA [illegible] using qPCR. Immunosuppression reduction is the cornerstone of effective management but is associated with a risk of acute rejection following treatment.

Keywords: BK polyomavirus nephropathy, kidney transplant, immune monitoring,

BKV is widely prevalent in general population with over 80% individuals having antibodies against BK virus.[3,4] The most common mode of transmission is through respiratory secretions, resulting in a mild self-limited respiratory infection.[5] Viral spread to other organs is believed to be via bloodstream and in immunocompetent individuals, it remains clinically silent in renal tubular epithelium.

high BK viral load in plasma >10,000 copies/mL for four weeks. Renal allograft biopsy remains the gold standard for diagnosing "definite" PVN.[6–12] Since the

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BK virus infection: an update on diagnosis and treatment

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BK Virus Nephropathy

Prevalence

- Among transplant recipients, it has been hypothesized that the intensity of immune suppression, determines the risk for BKV replication and progression to clinically significant disease
- Among kidney transplant recipients, BKV primarily causes tubulointerstitial nephritis and ureteral stenosis.
- The reported estimated prevalence of BKVN is 1 to 10 percent, with a mean of approximately 5 percent .
- Ureteral stenosis is less common among transplant patients .

VIROLOGY

BKV has been divided into four serological groups (I to IV) and genotypes, which may have different virulence potential .

Primary infections tend to occur early in childhood via feco-oral and/or respiratory exp ure .

the virus preferentially persists in the renal epithelium (transitional epithelium, renal tubular epithelium, and parietal epithelium of Bowman's capsule)

VIROLOGY

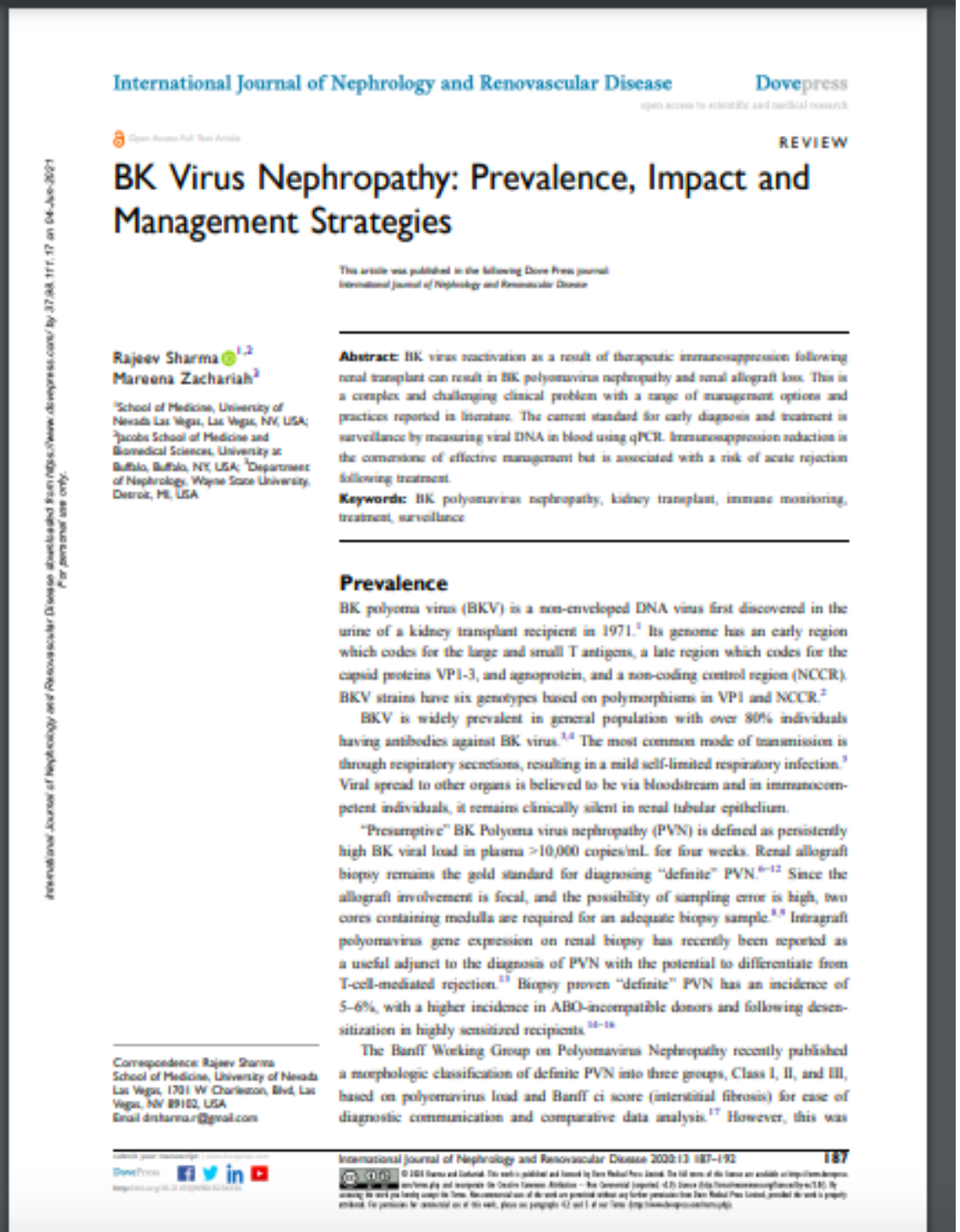
- In kidney transplant recipients with clinically significant BKPyV replication, mutations in noncoding control regions have been associated with high BKPyV viral loads . (20-fold higher plasma viral BK load).

- Serotype I is the most prevalent and is responsible for most human disease.

- Neutralizing antibodies to one serotype do not appear to confer protection against others.

VIROLOGY

- Intermittent BKV replication, manifested as asymptomatic viruria, occurs in immunocompetent individuals (up to 20 percent incidence of shedding).
- viruria is more common and higher grade in immunocompromised patients (10 to 60 percent).
- Patients with impaired cell-mediated immunity to be particularly at risk, including pregnant women (3 percent) . Viral shedding,disappears two weeks postpartum.



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BK Virus Nephropathy: Prevalence, Impact and Management Strategies

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Abstract: BK virus reactivation as a result of therapeutic immunosuppression following renal transplant can result in BK polyomavirus nephropathy and renal allograft loss. This is a complex and challenging clinical problem with a range of management options and practices reported in literature. The current standard for early diagnosis and treatment is surveillance by measuring viral DNA in blood using qPCR. Immunosuppression reduction is the cornerstone of effective management but is associated with a risk of acute rejection following treatment.

Keywords: BK polyomavirus nephropathy, kidney transplant, immune monitoring, treatment, surveillance

Prevalence

BK polyoma virus (BKV) is a non-enveloped DNA virus first discovered in the urine of a kidney transplant recipient in 1971.[1] Its genome has an early region which codes for the large and small T antigens, a late region which codes for the capsid proteins VP1-3, and agnoprotein, and a non-coding control region (NCCR). BKV strains have six genotypes based on polymorphisms in VP1 and NCCR.[2]

BKV is widely prevalent in general population with over 80% individuals having antibodies against BK virus.[3,4] The most common mode of transmission is through respiratory secretions, resulting in a mild self-limited respiratory infection.[5] Viral spread to other organs is believed to be via bloodstream and in immunocompetent individuals, it remains clinically silent in renal tubular epithelium.

"Presumptive" BK Polyoma virus nephropathy (PVN) is defined as persistently high BK viral load in plasma >10,000 copies/mL for four weeks. Renal allograft biopsy remains the gold standard for diagnosing "definite" PVN.[6–12] Since the allograft involvement is focal, and the possibility of sampling error is high, two cores containing medulla are required for an adequate biopsy sample.[8,9] Intragraft polyomavirus gene expression on renal biopsy has recently been reported as a useful adjunct to the diagnosis of PVN with the potential to differentiate from T-cell-mediated rejection.[13] Biopsy proven "definite" PVN has an incidence of 5–6%, with a higher incidence in ABO-incompatible donors and following desensitization in highly sensitized recipients.[14–16]

The Banff Working Group on Polyomavirus Nephropathy recently published a morphologic classification of definite PVN into three groups, Class I, II, and III, based on polyomavirus load and Banff ci score (interstitial fibrosis) for ease of diagnostic communication and comparative data analysis.[17] However, this was

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- BK polyoma virus (BKV) is a non-enveloped DNA virus first discovered in the urine of a kidney transplant recipient in 1971.
- 2[illegible] years later BK was recognized as a cause of interstitial nephritis and allograft failure in renal transplant recipients.

+ Risk

- The intensity of immunosuppression

(cellular immunity) is the dominant risk factor for BKPyV replication and disease.

- replication rates are higher in the early posttransplant period and following treatment for allograft rejection when immunosuppression peaks.

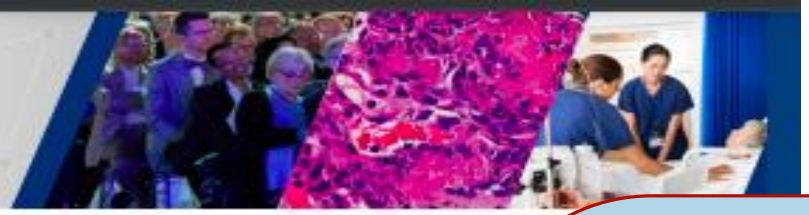
+ Risk

- Several studies have suggested that certain drugs particularly tacrolimus_ may be associated with an increased relative risk .
- [mTOR] inhibitors may be associated wi[illegible]a lower relative risk .
- BKPyV replication and BKPyVAN have occurred in patients receiving nearly all immunosuppressive drugs and their combinations.

+Risk

- In one cohort study of over 20,000 kidney pairs, factors associated with BKPyVAN included:

- age <18 or ≥60 years
- male sex
- ureteral stent placement
- ≥4 HLA-A, -B, or -DR mismatches;
- rejection or delayed graft function
- use of an antibody-depleting agent for induction
- specific HLA-C alleles
- BKPyV polymorphisms



BK Virus Nephropathy

Deirdre Sawinski[1] *and Jennifer Trofe-Clark*[1,2]

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Introduction

BK virus nephropathy is a serious complication of kidney transplantation. Although 10%–30% of kidney recipients have BK viremia, nephropathy occurs in approximately 2% (1). Nephropathy is most common early after transplant when immunosuppression is at its peak. Patients are often asymptomatic, and the diagnostic standard is biopsy (1). There are no effective viral therapies for BK, and therefore, recipients with BK nephropathy are at great risk of graft loss.

Outcomes and Risk Factors

Although uncommon, BK nephropathy represents a significant threat to allograft survival. Registry data showed that 3-year graft survival was significantly lower in recipients with BK nephropathy (79% versus 90%; $P<0.001$) (2). Two recent biopsy series reported and C4d staining was positive in only 10% of peritubular capillaries.

Is Screening Useful?

Universal, prospective screening for BK in the urine or plasma is recommended to identify early viral replication, permit intervention, and prevent progression to nephropathy or allograft loss. The optimal frequency and screening methodology remain undefined. Guidelines unanimously recommend greater screening intensity in the first year and whenever kidney dysfunction is investigated (1,5,6). We screen all kidney recipients using plasma BK PCR at 1, 3, 6, 12, and 24 months; we also screen any patients with unexplained allograft dysfunction. Plasma PCR is the preferred modality, because the correlation with nephropathy is better than with urine PCR testing. A BK viral load in the plasma of ≥10,000 copies/ml or

kind of immunosuppressive drugs
older age
male gender
ureteral trauma
DM
DGF
use of ATG
CMV infection
treatment for acute rejection
use of GC maintenance therapy
specific (HLA)-C loci

pathogens

MDPI

Review

BK Virus-Associated Nephropathy after Renal Transplantation

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Table 1. Reported risk factors for BKVAN.

Donor factors	Deceased donor [21]
	BKV viruria [22]
	High BKV antibody titers [23,24]
	Female gender [21]
	Degree of HLA mismatches [21,25]
	Positivity of HLA A9 [26], G 3′UTR-4 [27]
	Negativity of HLA C7 [28,29]
Recipient factors	Older age [21]
	Male gender [21]
	ABO incompatibility [30]
	History of hemodialysis [31]
	Low BKV antibody titers [24]
	African American [32]
	Diabetes [21]
	Positivity of HLA A2 [26], G 3′UTR-4 [27]
	Negativity of HLA C7 [28], B51 [33]
Transplant factors	Acute rejection and antirejection treatment [25,34,35]
	Delayed graft function [36]
	Cold ischemia time [37]
	Steroid exposure [38]
	Tacrolimus levels [38]
	Tacrolimus and/or MMF-based maintenance immunosuppression [21,31,39]
	Ureteric stent replacement [40]

+ RISK

- Studies have demonstrated that the source of BKV in the recipient is the donor in the majority of cases (rather than reactivation of latent recipient BKV infection) .
- high risk serostatus (kidney transplant from a BKPyV-seropositive donor to a seronegative recipient).
- pretransplant viruria in the donor is an independent risk factor for posttransplant BKV infection.

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BK virus infection and outcome following kidney transplantation in childhood

James McCaffrey[1]✉, Vijesh J. Bhute[2] & Mohan Shenoy[3]

BK virus associated nephropathy (BKN) is an important cause of kidney allograft failure. In a cohort of paediatric kidney transplant recipients, we aimed to understand the incidence and clinical outcome associated with BKN, as well as identify risk factors for BKN and BK viraemia development. We retrospectively analysed all patients who received a kidney transplant and received follow up care in our centre between 2009–2019. Among 106 patients included in the study (mean follow up 4.5 years), 32/106 (30.2%) patients experienced BK viraemia. The incidence of BKN was 7/106 (6.6%). The median time of BK viraemia development post-transplant was 279.5 days compared to 90.0 days for BKN. Development of BKN was associated with younger age at transplantation ($p = 0.013$). Development of BK viraemia was associated with negative recipient serology for cytomegalovirus (CMV) at time of transplantation ($p = 0.012$) and a higher net level of immunosuppression ($p = 0.039$). There was no difference in graft function at latest follow up between those who experienced BKN and those without BKN. This study demonstrates that BK virus infection is associated with younger age at transplantation, CMV negative recipient serostatus and higher levels of immunosuppression. Judicious monitoring of BK viraemia in paediatric transplant recipients, coupled with timely clinical intervention

2021

106 patients
analysed all patients who received a kidney transplant and received follow up care between 2009–2019.

This study demonstrates that BK virus infection is associated with younger age at transplantation, CMV negative recipient serostatus and higher levels of immunosuppression.

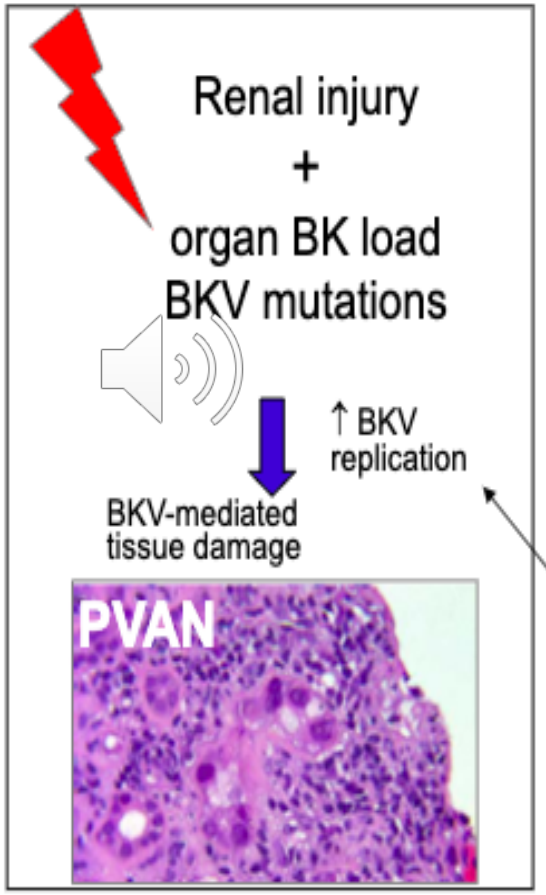
monitoring of BK viraemia in paediatric transplant recipients, coupled with timely clinical intervention can result in similar long-term outcomes for BKN patients compared to controls

- RISK

- some factors have been associated with decreased risk of BKPyVAN.
- In one cohort of 407 living kidney donor-recipient pairs, recipient HLA-B51 positivity was associated with an approximate fivefold reduction in BKPyVAN (HR 0.18, 95% CI 0.04-0.73) .
- Polycystic kidney disease has also been associated with a lower risk of BKPyVAN

Pathogenesis

BKV nephropathy after kidney Tx: pathogenesis



Immunosuppression load:
triple vs. double therapy
Binet et al. Transplantation 1999
Hirsch et al. Transplantation 2005

±

Lack of immune memory:
BK seronegativity
Ginevri et al. Transplantation 2003
Smith et al. Am J Transplant 2004

Failure of immune surveillance

Pathogenesis

- Viruria is detected in 25 to 30 and viremia in 12 percent of kidney transplant recipients.

- the development of nephropathy in a stereotypical pattern of viruria, followed by viremia, followed by BKPyV-associated nephropathy (BKPyVAN).

Pathogenesis

- Approximately 1 to 10 percent of kidney transplant recipients will develop BKPyVAN .
- Historically, BKPyVAN was associated with graft loss rates that exceeded 50 percent .

PATHOGENESIS

- Loss of cellular immune control over latent viral infection is the key initiating event in the pathogenesis of (BKPyVAN).
- BKPyV causes persistent infection in the renal and uroepithelium (transitional epithelium, renal tubular epithelium, and parietal epithelium of Bowman's capsule)
- Control of this persistent infection is dependent on CD4+ and CD8+ T cell immunity .
- When immune control is disrupted BKPyV can begin to actively replicate.

PATHOGENESIS

- As viral replication persists, injury to the renal tubular epithelium results from direct viral invasion. Subsequent inflammation and fibrosis lead to tubular atrophy, necrosis, and nephron loss .
- Preliminary data suggest that the renal allograft inflammatory profile in BKPyVAN is similar to that seen in acute cellular rejection and involves both virus- and allograft-directed immune injury.

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BK virus infection: an update on diagnosis and treatment

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ABSTRACT

BK virus, first isolated in 1971, is a significant risk factor for

BK VIRUS

The BK virus was first isolated from the urine of a renal trans-

In the setting of immunosuppression, the virus reactivates and begins to replicate, starting with tubular cell lysis and viruria.

The BK virus then multiplies in the interstitium and crosses into the peritubular capillaries, causing viremia and eventually invading the allograft, leading to various tubulointerstitial lesions and BKVN.

The outcome depends on the degree of damage, inflammation and fibrosis.

Nephropathy

- *Viruria is the earliest manifestation of BKPyV infection in kidney transplant recipients, affecting approximately one-quarter to one-third of patients during the first year following transplantation .*
- *viruria is a sensitive marker for progression to (BKPyVAN) .*
- *Urine decoy cells (renal tubular or uroepithelial cells containing intranuclear viral inclusions*

Nephropathy

- BKPyVAN can occur years after transplantation .
- The incidence of late BKPyVAN appears to be highest in patients with multi-organ transplants.
- Without resolution of infection, progressive renal allograft dysfunction and graft loss can ensue over a period of months.
- early infection triggers interstitial inflammation, which then progresses to fibrosis and tubular injury.

Nephropathy

- The development of alloimmunity and acute rejection (following reduction of immunosuppression in response to BKPyV replication) may further contribute to allograft dysfunction and potentially graft loss .
- The leading cause of graft loss was BKPyVAN, occurring in 45 percent, followed by acute and chronic rejection in 25 and 12 percent.

Other issues

- There is a putative link between BKPyV and the development of genitourinary cancers, largely based upon viral-associated oncogenesis in animal models and the ability of the virus to transform cells in vitro.
- However, a causal role for BKPyV and human malignancies has not been definitively established.

IMPACT

- tubulointerstitial nephritis
- rarely ureteral stenosis .
- Hemorrhagic and nonhemorrhagic cystitis may occur in hematopoietic cell transplant recipients is rarely observed among kidney transplant recipients .
- less common manifestations that have been associated with BKV, including vasculopathy, meningoencephalopathy, retinitis, pneumonitis, hepatitis, SLE,Guillain-Barré syndrome, and a variety of neoplasms.

Manifestation

- Patients with BKVN most commonly present with an asymptomatic acute or slowly progressive rise in the serum creatinine or occasionally as an unsuspected finding on surveillance renal allograft biopsy .
- there are typically no clinical signs or symptoms of infection.
- the onset of nephritis may occur as early as six days posttransplantation or as late as five years .

lab

- Among patients with BKVN, laboratory evaluation usually reveals an elevated serum creatinine.
- Routine urinalysis may reveal pyuria, hematuria, and/or cellular casts consisting of renal tubular cells and inflammatory cells, findings consistent with interstitial nephritis.
- the urinalysis may also be normal

Diagnosis

- BKVN is first suspected clinically in the patient with clinical findings suggestive of interstitial nephritis.
- there are **NO** clinical features of tubulointerstitial nephritis that are unique to BKV infection.
- A definitive diagnosis of BKVN requires findings on renal biopsy .

BK NEPHROPATHY IN THE NATIVE KIDNEY

- One case series reported eight immunocompromised patients with BKVN, including six with hematologic malignancies (three with bone marrow transplant), one patient with a lung transplant, and one patient with immunodeficiency secondary to tuberculosis and diabetes.
- All patients presented with AKI ; none had significant proteinuria, and only one had an active urine sediment with hematuria and leukocyturia. Only one patient had decoy cells on urine microscopy.
- All patients had characteristic histologic findings on kidney biopsy and positive serum and urine PCR for BKV.

BK NEPHROPATHY IN THE NATIVE KIDNEY

- Four patients were treated with cidofovir and two with leflunomide, but immunosuppressive therapy was not decreased in any patient.
- Although serum BK viral loads decreased, AKI worsened in all patients, with the development of ESRD in two patients by three months.

Screening

- Posttransplant screening

- We recommend routine screening for (BKPyVAN) for all kidney transplant recipients in the early posttransplant period.

Screening

- We screen patients with a quantitative plasma BKPyV (PCR; viral load) at the following time points:
- Monthly for the first six months following transplant, then every three months until two years posttransplant, and then annually until five years posttransplant

HOW

- Testing methods:

- Plasma quantitative PCR
- Urine quantitative PCR
- Urine cytology
- Renal allograft biopsy

سپاس