
In the Name of God

BK NEPHROPATHY

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INTRODUCTION

- BK polyomavirus (BKPyV) is a small double-stranded DNA virus that establishes lifelong infection in the renal tubular and uroepithelial cells of most of the world's population.
- For the majority, infection is quiescent and benign.

- In immunocompromised patients, especially among those with deficiencies in cellular immunity, BKPyV can reactivate.
- For some, this can lead to BKPyV-associated nephropathy (BKPyVAN).
- Polyomavirus-associated nephropathy in kidney transplant recipients has also been rarely reported with the JC polyomavirus (JCPyV).

- Reactivation is frequently subclinical.
- Although it may manifest with acute kidney injury (AKI) and is associated with allograft dysfunction and premature allograft loss.
- Thus, screening for reactivation is recommended for all kidney transplant recipients after transplantation.

- For those with clinically significant reactivation, reduction of immunosuppression is the cornerstone of management, since there is no specific antiviral or immunomodulatory therapy sufficiently effective for routine use.

EPIDEMIOLOGY

PREVALENCE

- BK polyomavirus (BKPyV) is a ubiquitous virus with a worldwide seroprevalence of approximately 80 to 90 percent.
- Primary infection is typically acquired during childhood, possibly via fecal-oral or respiratory transmission.
- Following primary infection, the virus establishes lifelong infection in renal tubular and uroepithelial cells.

- Among kidney transplant recipients, reactivation of latent infection or transmission of new infection via the donor kidney can lead to viruria (detection of intact virus or virus components in urine), viremia (typically by detection of viral DNA in blood), or allograft nephropathy (demonstration of virus or virus components in allograft tissue).
- Viral replication most commonly occurs during the first year after transplantation when cellular immunity is most suppressed.

- Viruria are detected in approximately 25 to 50 percent of kidney transplant recipients.
- Viremia are detected in approximately 10 to 20 percent of kidney transplant recipients.
- Approximately 1 to 10 percent of kidney transplant recipients will develop BKPyVAN.

RISK FACTORS FOR VIRAL REPLICATION

- The intensity of immunosuppression (particularly suppression of cellular immunity) appears to be a 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 intensity is highest.

- No specific immunosuppressive drug or regimen has been definitively associated with an increased risk for clinically significant BKPyV infection.

DRUGS

- Several studies have suggested that certain drugs (particularly tacrolimus) may be associated with an increased relative risk.
- The mammalian [mechanistic] target of rapamycin [mTOR] inhibitors) may be associated with a lower relative risk.

IMPORTANT RISK FACTORS

1. High risk serostatus (ie, kidney transplant from a BKPyV-seropositive donor to a seronegative recipient),
2. Impaired immune response to BKPyV,
3. Donor BKPyV viruria prior to transplant.

RISK FACTORS ASSOCIATED WITH AN INCREASED RISK OF DISEASE SEVERITY

1. Older age,
2. Ureteral stent placement,
3. ABO incompatibility,
4. Rejection or ischemia of the transplanted kidney,
5. Delayed graft function,
6. HLA mismatch,
7. Specific HLA-C alleles,
8. BKPyV polymorphisms,
9. Transplantation from an HCV-positive donor.

- In one cohort study of over 20,000 mate kidney pairs, factors associated with BKPyVAN included:
- 1. Use of an antibody-depleting agent for induction;
- 2. Age <18 or ≥60 years;
- 3. Male sex;
- 4. ≥4 HLA-A, -B, or -DR mismatches;
- 5. Acute allograft rejection.

FACTORS HAVE BEEN ASSOCIATED WITH A 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 (hazard ratio [HR] 0.18, 95% CI 0.04-0.73).
- Polycystic kidney disease has also been associated with a lower risk of BKPyVAN.
- The mammalian [mechanistic] target of rapamycin [mTOR] inhibitors) may be associated with a lower relative risk.

Transplant-related:

Immunosuppression

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

Graft-related

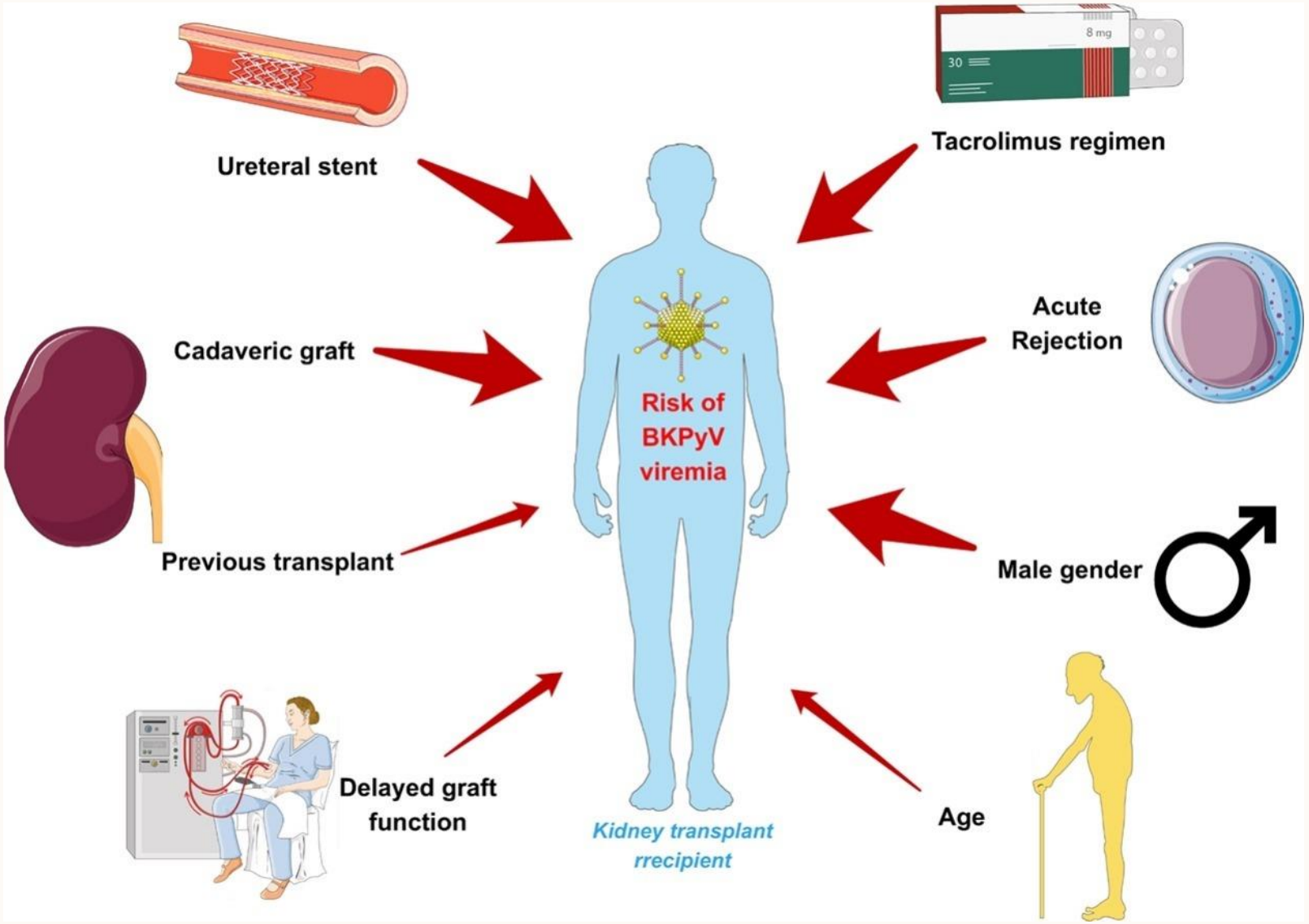
- Prior treatment of acute rejection
- Prolonged cold/warm ischemia timing
- Delayed graft function
- Ureteric stent placement
- Renal injury (immune related,.. etc.)

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


Ureteral stent
Tacrolimus regimen
8 mg
30
Cadaveric graft
Acute Rejection
Risk of BKPyV viremia
Previous transplant
Male gender
Delayed graft function
Age
Kidney transplant rrecipient

PATHOGENESIS

- Insufficient cellular immune control is presumed to be an important part of BK polyomavirus (BKPyV)-associated nephropathy (BKPyVAN) pathogenesis.
- After primary infection, which typically occurs in childhood, BKPyV maintains persistent infection in the renal and uroepithelium (transitional epithelium, renal tubular epithelium, and parietal epithelium of Bowman's capsule) of most individuals.
- Control of this persistent infection is dependent on CD4+ and CD8+ T cell immunity.

- When immune control is disrupted (as with immunosuppressive drugs), BKPyV can begin to actively replicate.

CLINICAL MANIFESTATIONS

- In kidney transplant recipients, BK polyomavirus (BKPyV) replication typically develops in stages: viruria followed by viremia and then, if viral replication persists, nephropathy can ensue.

BKPYV REPLICATION TYPICALLY PROGRESS THROUGH THREE STAGES

1. Asymptomatic viruria occurs in approximately one-quarter to one-third of patients during the first posttransplant year.
2. Viremia follows viruria in approximately one-half of patients.
3. In a subset of viremic patients, viral replication progresses leading to damage to renal tubular epithelium and BKPyV-associated nephropathy (BKPyVAN).

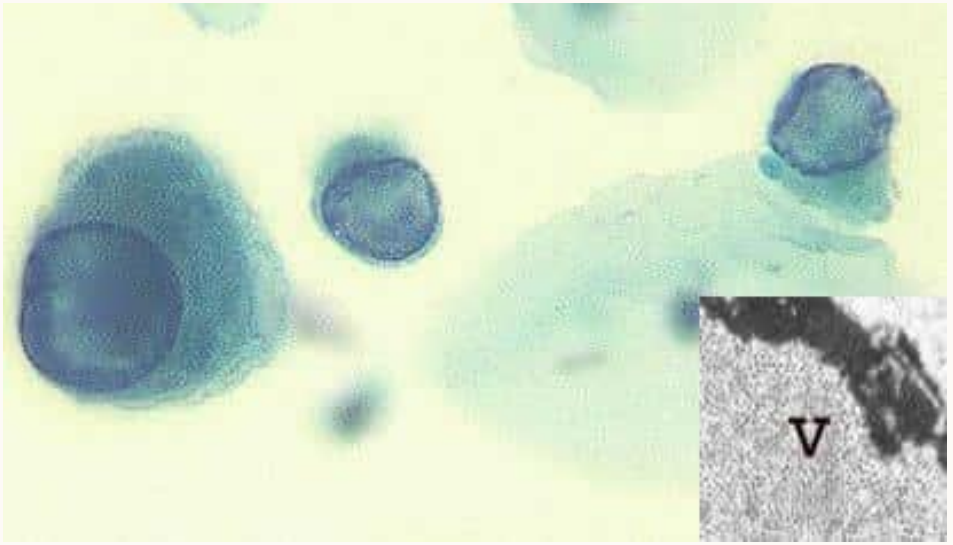
VIRURIA

- Viruria is the earliest manifestation of BKPyV infection in kidney transplant recipients, affecting approximately one-quarter to one-half of patients during the first year following transplantation.
- For most, viruria is asymptomatic, detected only by screening, and does not progress to viremia.

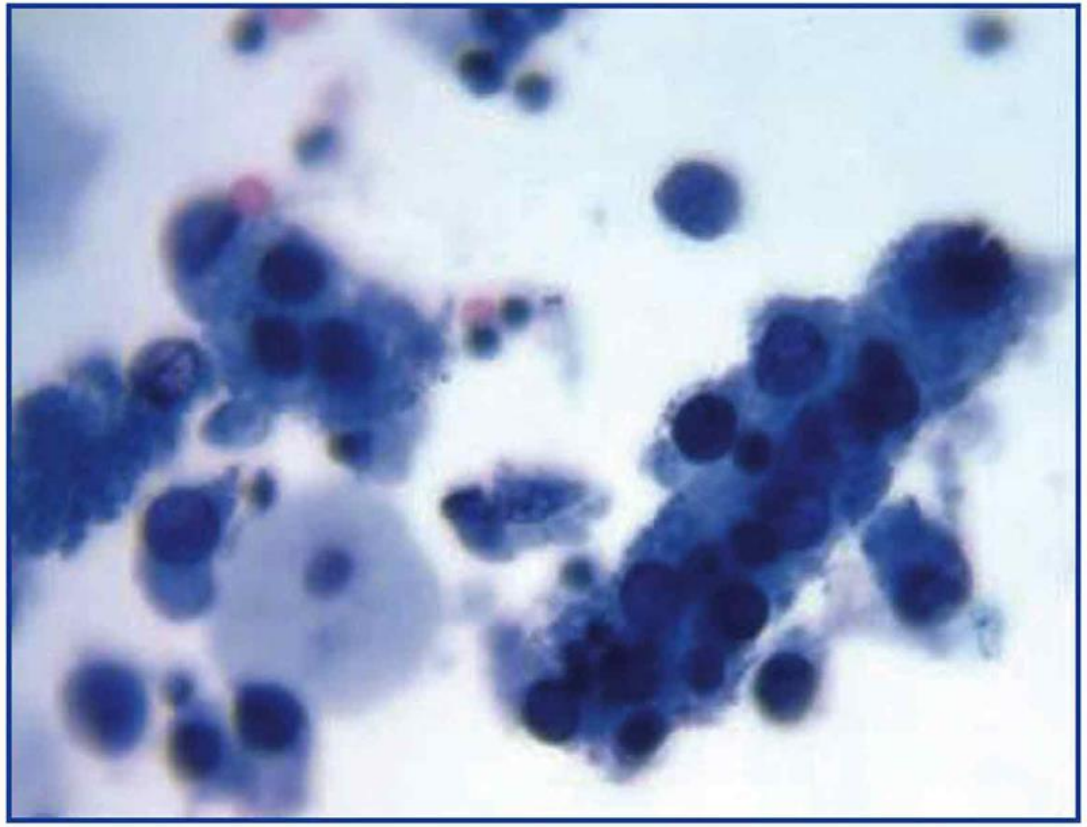
- Shedding of BKPyV in the urine (as detected by highly sensitive polymerase chain reaction [PCR] methods) is common among otherwise healthy older adult patients, pregnant women, and others with suppressed cellular immunity and is generally without clinical consequence.
- Urine decoy cells (renal tubular or uroepithelial cells containing intranuclear viral inclusions), which typically represent higher-level viruria, may be present at this stage.

URINE MICROSCOPY SHOWING DECOY CELLS

- Urine cytology sediment demonstrates 3 "decoy" cells, characterized by large viral nuclear inclusions that replace the normal chromatin (Papanicolaou stain).
- The nuclear inclusion is formed by dark, smudged material representing thousands of newly formed virions (V).
- Electron microscopy (insert) shows the contrast between the inclusion (V) and the darker surrounding chromatin.



DECOY CELL



VIREMIA

- Viremia may follow viruria in a few weeks and occurs most frequently in those with high urine viral loads and sustained viruria.
- Viremia is detected in 10 to 20 percent of recipients in the first six months posttransplantation and in 5 to 10 percent of recipients thereafter.
- As with viruria, viremia is typically asymptomatic.
- However, viremia has a greater predictive value than viruria for progression to BKPyVAN.

- Viremia is present in nearly all patients with BKPyVAN and has a positive predictive value of approximately 40 to 65 percent for the development of BKPyVAN.
- Because BKPyVAN can quickly follow viremia (eg, within one to two weeks) and damage to the graft can be irreversible, viremia is a generally accepted indication to reduce immunosuppression in kidney transplant recipients.

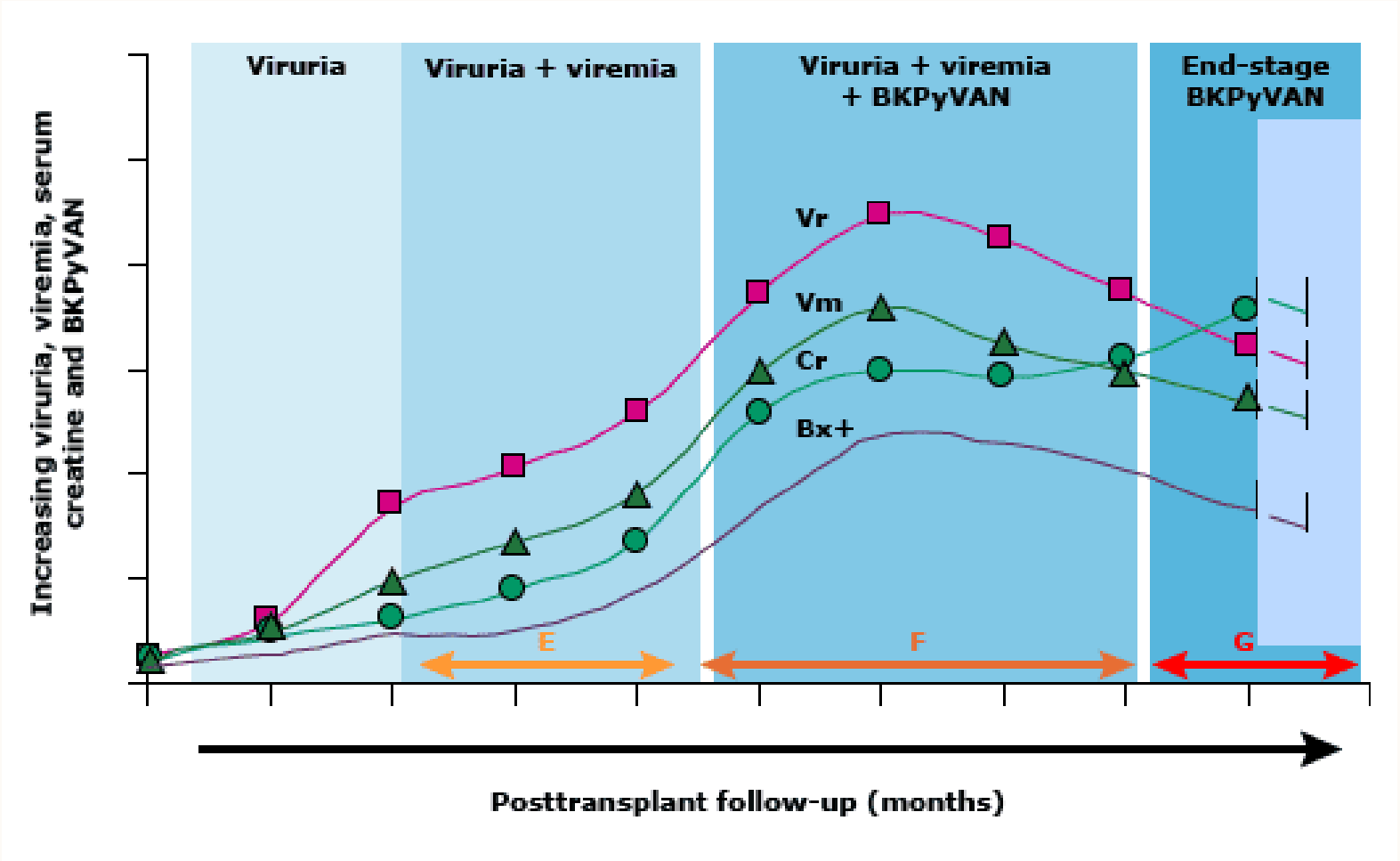
- Higher viral loads and sustained viremia have greater predictive value for concomitant or progression to biopsy-confirmed BKPyVAN.

BKPyV-ASSOCIATED NEPHROPATHY (BKPyVAN)

- The incidence of BKPyVAN is highest in the first two to six months posttransplant.
- While the majority of cases occur in the first posttransplant year, BKPyVAN can occur years after transplantation.
- The incidence of late BKPyVAN appears to be highest in patients with multi-organ transplants and is possibly related to the more intensive immunosuppressive regimens used for these patients.

- Without resolution of infection, progressive kidney allograft dysfunction and graft loss can ensue over a period of months.
- Within the allograft, early infection triggers interstitial inflammation, which then progresses to fibrosis and tubular injury.
- Urinalysis may reveal pyuria, hematuria, and/or cellular casts consisting of renal tubular cells and inflammatory cells, or may be normal.

TYPICAL COURSE OF VIRURIA, VIREMIA, AND BK-INDUCED NEPHROPATHY



(E) PREEMPTIVE INTERVENTION

- In patients with Vr and Vm, progressive and customized decrease in immunosuppression before significant renal scarring has occurred leads to resolution of the infection in 85 to 90% of cases, with long-term preservation of graft function.
- Risk of acute rejection is low (10 to 15%).
- Intervention is not indicated in the absence of Vm (ie, Vr only).

(F) OBLIGATORY INTERVENTION

- Late diagnosis and intervention once graft dysfunction is evident decreases the likelihood of viral clearance.
- This stage is associated with higher rates of premature graft loss (30 versus 10%).

(G) INEFFECTUAL, LATE INTERVENTION

- The late stage of BKPyVAN resembles clinically and histologically end-stage kidney disease from other causes.

OTHER MANIFESTATIONS

- Hemorrhagic cystitis is a rare manifestation of BKPyV infection in kidney transplant recipients but is the most commonly reported manifestation of BKPyV infection among hematopoietic cell transplant recipients.

- 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.

SCREENING AND DIAGNOSIS

POST TRANSPLANT SCREENING

- We recommend routine screening for BK polyomavirus (BKPyV)-associated nephropathy (BKPyVAN) for all kidney transplant recipients in the early posttransplant period.
- Observational data suggest that screening and preemptive reduction in immunosuppression for patients with clinically significant BKPyV viremia prevent progression to BKPyVAN in the majority of patients.

- The optimal screening strategy has not been determined, and approaches vary among transplant centers.

- We screen patients with a quantitative plasma BKPyV polymerase chain reaction (PCR; ie, viral load) at the following time points:
- 1. Monthly for the first nine months following transplant, then every three months until two years posttransplant, and then annually until five years posttransplant.
- 2. Whenever kidney allograft dysfunction occurs.
- 3. When an allograft biopsy is performed for allograft dysfunction.

- This is important since BKPyV involvement of the allograft can be patchy and preferentially involves the medulla, which can lead to a falsely negative biopsy.

- The threshold plasma BKPyV viral load that is considered positive or clinically significant varies according to the particular assay used.
- In general, levels >1000 copies/mL are considered positive in most assays.
- Levels >10,000 copies/mL correlate with biopsy-confirmed BKPyVAN.

- For patients with viremia (eg, viral loads >1000 copies/mL) and normal allograft function, we typically reduce immunosuppression and monitor the viral load every two to four weeks thereafter to ensure that it is downtrending.

- For patients with viremia and new-onset allograft dysfunction, we generally reduce immunosuppression and monitor viral loads every two to four weeks thereafter when the clinical picture suggests that BKPyVAN is the most likely cause.

- We consider a kidney allograft biopsy if the cause for kidney allograft dysfunction is uncertain or if kidney dysfunction and/or viremia fail to resolve despite reducing immunosuppression.

- Our approach is generally consistent with the Kidney Disease: Improving Global Outcomes (KDIGO), American Society of Transplantation Infectious Diseases Community of Practice (AST-IDCOP), and Second International Consensus guidelines.

TESTING METHODS

PLASMA QUANTITATIVE PCR

- Quantification of plasma BKPyV DNA by real-time polymerase chain reaction (PCR) is the preferred screening test for BKPyVAN at most transplant centers.
- The detection of BKPyV viremia by plasma quantitative PCR is both highly sensitive (100 percent) and specific (88 percent) for the diagnosis of BKPyVAN and has a higher positive predictive value for BKPyVAN than the detection of viruria by urine quantitative PCR or urine cytology (50 to 60 percent versus 40 and 29 percent, respectively).

- In addition, following the initial detection of viremia, plasma PCR can be used to monitor the patient's response to therapy since a decrease in BKPyV viremia usually occurs soon after a reduction in immunosuppression and precedes a decrease in viruria by weeks to months.

- There are no clearly established threshold levels for BKPyV viremia that predict BKPyVAN.
- However, most experts agree that a BKPyV viral load of ≥10,000 copies/mL, particularly when sustained for more than three weeks' duration, is highly suggestive of BKPyVAN (“Presumptive" BKPyVAN).

URINE QUANTITATIE PCR

- We do not use quantitative PCR of the urine for BKPyV DNA to screen for BKPyVAN.
- Some transplant centers prefer to screen with urine polymerase chain reaction (PCR), given the high sensitivity and less invasive nature of this test, and proceed to plasma PCR for those with viruria.

- However, patients who are found to have viruria require confirmation with quantitative plasma PCR, since approximately one-half of patients with BKPyV viruria will not develop viremia or BKPyVAN.
- As such, the cost effectiveness of this approach has been questioned.

- Furthermore, urine PCR for BKPyV DNA is not as useful as plasma PCR for monitoring the response to therapy.
- However, some studies suggest that the detection of high-grade viruria might be helpful to predict clinically significant viremia.

URINE CYTOLOGY

- Cytologic examination of the urine, which may reveal BKPyV-infected cells, is infrequently used to screen for BKPyVAN.
- Although the presence of characteristic cytopathologic changes in infected cells (which have been called decoy cells) is strongly suggestive of BKPyV infection, urine cytology is less sensitive and specific for the diagnosis of BKPyVAN compared with plasma quantitative PCR.

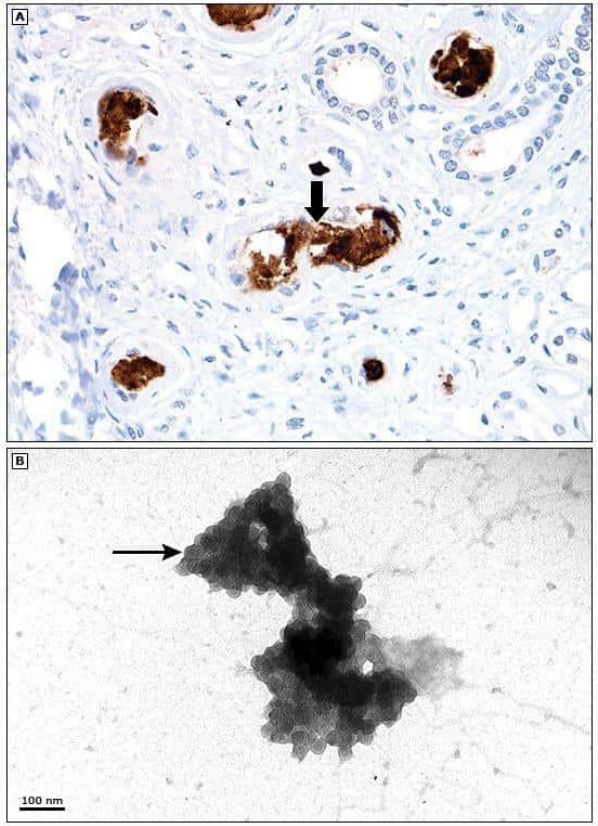
ELECTRON MICROSCOPY OF URINE

- Negative-staining electron microscopy of the urine of patients with BKPyVAN often reveals the presence of cast-like, three-dimensional polyomavirus aggregates, termed Haufen.
- Haufen form in injured tubules with BKPyV replication and a high intratubular uromodulin concentration and are excreted into the urine similar to other urinary casts.

- In one cohort study of >300 kidney transplant recipients, the detection of Haufen in voided urine had a sensitivity, specificity, negative predictive value, and positive predictive value for biopsy-proven BKPyVAN of greater than 95 percent, suggesting that this may be a noninvasive way to diagnose BKPyVAN.

- However, the urinary Haufen test requires electron microscopy.
- Thus, it is not a widely used screening test.
- It may be used in certain clinical scenarios, such as in pediatric patients or when a kidney allograft biopsy cannot be safely performed.

HAUFEN



SCREENING TESTS FOR BK POLYOMAVIRUS-ASSOCIATED NEPHROPATHY (BKPYVAN)

Method	Sensitivity* (%)	Specificity * (%)	PPV*	NPV*	Advantage	Disadvantage
Plasma quantitative PCR (preferred)	100	88	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

SCREENING TESTS FOR BK POLYOMAVIRUS-ASSOCIATED NEPHROPATHY (BKPYVAN)

Method	Sensitivity* (%)	Specificity* (%)	PPV*	NPV*	Advantage	Disadvantage
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

SCREENING TESTS FOR BK POLYOMAVIRUS-ASSOCIATED NEPHROPATHY (BKPYVAN)

Method	Sensitivity * (%)	Specificity * (%)	PPV*	NPV*	Advantage	Disadvantage
Urine decoy cells	100	71	Low	High	•Lower cost	•Decoy cells identification needs experience •Does not distinguish among polyomaviruses (ie, JCPyV versus BKPyV)

SCREENING TESTS FOR BK POLYOMAVIRUS-ASSOCIATED NEPHROPATHY (BKPYVAN)

Method	Sensitivity* (%)	Specificity* (%)	PPV*	NPV*	Advantage	Disadvantage
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

KIDNEY ALLOGRAFT BIOPSY

- Kidney allograft biopsy is the gold standard for diagnosing BKPyVAN, assessing its severity, and evaluating for concomitant processes.
- However, because biopsy is invasive and sampling error can occur, a presumptive diagnosis is often made based upon the presence of significant viremia (plasma BKPyV viral load ≥10,000 copies/mL).

- A definitive diagnosis of BKPyVAN requires the following findings on kidney biopsy:
- 1. Characteristic cytopathic changes.
- **plus**
- 2. Positive immunohistochemistry tests using antibodies directed specifically against BKPyV or against the cross-reacting SV40 large T antigen.

- Positive SV40 staining is useful as it is associated with a specificity of almost 100 percent for polyomavirus nephropathy (PVN).
- It does not distinguish between BKPyV- and JC virus (JCV)-associated cases.

- Because of the focal nature of early BKPyVAN, the diagnosis may be missed on one-third of biopsies.
- As a result, at least two biopsy cores, preferably including medulla, should be examined.
- Medullary tissue should be included because BKPyV is more likely to be present in the medulla.
- If the initial biopsy does not confirm BKPyVAN, a repeat biopsy should be considered.

HISTOLOGIC FINDINGS

- BKPyVAN is associated with characteristic histologic findings on kidney biopsy.
- Since viral cytopathic changes can also be observed with cytomegalovirus (CMV), adenovirus, and herpes simplex virus (HSV) infections, the morphologic changes may not be pathognomonic.

CHARACTERISTIC HISTOLOGIC FINDINGS ON KIDNEY BIOPSY

- 1. Intranuclear basophilic viral inclusions without a surrounding halo.
- CMV has cytoplasmic inclusions.
- HSV has both intranuclear and cytoplasmic inclusions.

CHARACTERISTIC HISTOLOGIC FINDINGS ON KIDNEY BIOPSY

- 2. Anisonucleosis, hyperchromasia, and chromatin clumping of infected cells.
- 3. Interstitial mononuclear or polymorphonuclear cell infiltrates in the areas of tubular damage.

CHARACTERISTIC HISTOLOGIC FINDINGS ON KIDNEY BIOPSY

- 4. Tubular injury, which is characterized by tubular cell apoptosis, cell drop out, desquamation, and flattened epithelial lining.
- 5. Tubulitis, which is manifested by lymphocyte permeation of the tubular basement membrane.
- When extensive, it is difficult to differentiate BKPyVAN from allograft rejection.

CHARACTERISTIC HISTOLOGIC FINDINGS ON KIDNEY BIOPSY

- 6. With electron microscopy, intranuclear viral inclusions (with a diameter size of 30 to 50 nm) and tubular damage characterized by tubular cell necrosis, prominent lysosomal inclusions, and luminal protein and cellular casts.

DISTINGUISHING BKPyVAN FROM REJECTION

- Allograft rejection may closely resemble BKPyVAN on kidney biopsy.
- Distinguishing BKPyVAN from allograft rejection is important since treatment for presumed rejection with increased immunosuppression (without concomitant reduction in maintenance immunosuppression) may result in allograft loss if BKPyVAN is present.

- BKPyVAN is generally distinguished from rejection by the presence of BKPyV inclusions and immunohistologic or in situ hybridization evidence of virally infected cells, which are usually tubular epithelial cells, rather than podocytes or endothelial cells.
- It is important to correlate the histologic findings with PCR evidence of viremia.

- In general, the presence of extensive tubulitis in areas remote from the viral cytopathic changes suggests that acute rejection is present, in addition to BKPyVAN.
- The combined presence of endarteritis, fibrinoid vascular necrosis, glomerulitis, and C4d deposits along peritubular capillaries is conclusive evidence of concurrent rejection.
- Although some patients with BKPyVAN without concurrent rejection may have C4d deposits in the tubular basement membrane.

- Among some patients, it may only be possible to distinguish the effects of BKPyV viral infection from those of rejection by empirically altering the immunosuppressive regimen and observing the clinical response.

PLASMA DONOR-DERIVED CELL-FREE DNA

- Donor-derived cell-free DNA (dd-cfDNA) is released into the bloodstream from dead cells in the kidney allograft, particularly if the allograft is injured.
- Several studies have shown that elevated plasma dd-cfDNA levels are associated with acute allograft rejection.
- Some centers use dd-cfDNA levels to monitor for early acute rejection.

- One study reported that higher dd-cfDNA levels correlated with higher BKPyV viral loads and biopsy-diagnosed BKPyVAN.
- Suggesting that dd-cfDNA levels might be useful in monitoring for progression from BKPyV viremia to BKPyVAN.
- However, additional studies are needed to define a role for dd-cfDNA in the diagnosis of BKPyVAN.

TREATMENT

OVERVIEW OF TREATMENT

- Since there are no specific antiviral therapies for BK polyomavirus (BKPyV)-associated nephropathy (BKPyVAN), the cornerstone of management is to decrease immunosuppressive medications.
- In general, this approach applies to both the prevention of BKPyVAN in patients with BKPyV viremia detected by routine screening and the treatment of patients with established BKPyVAN.

- The optimal approach to reducing immunosuppression has not been defined.
- Protocols vary among transplant centers and are often individualized.

- The initial approach of decreasing immunosuppressive medications is effective in most patients.
- For patients who have progressive allograft dysfunction, despite a maximal decrease in immunosuppressive therapy for a period of several weeks to months, we may try agents that may have antiviral and/or immunomodulatory activity, such as intravenous immune globulin (IVIG).
- However, the efficacy of this approach has not been proven.

- We do not use leflunomide, cidofovir, or quinolone antibiotics.

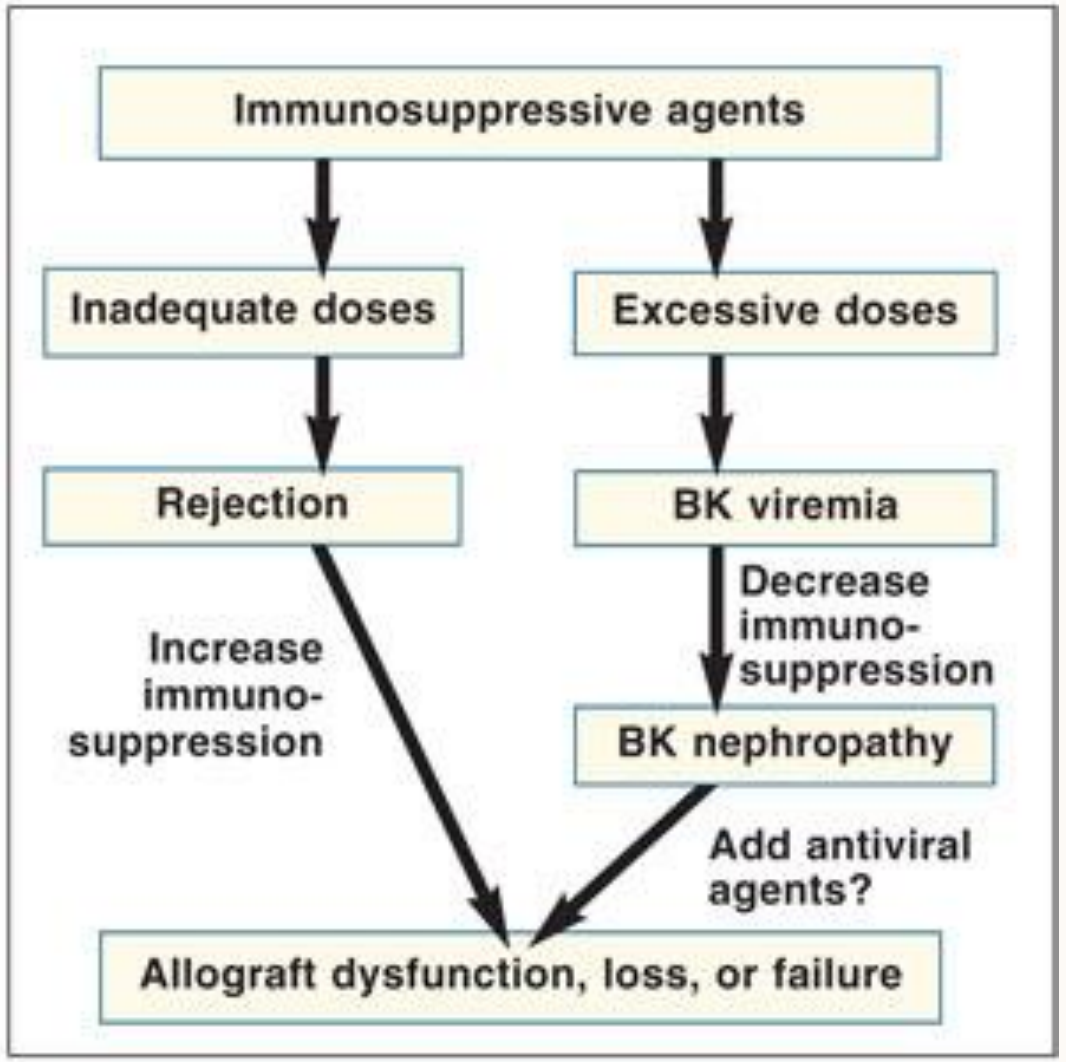


Figure 1. Effects of immune-suppression imbalance.

REDUCTION OF IMMUNOSUPPRESSION

- We recommend reducing maintenance immunosuppression for most kidney transplant recipients with detectable BKPyV viremia or biopsy-proven BKPyVAN.
- The goals of reducing immunosuppression are to restore immunity against BKPyV without triggering allograft rejection.
- Approaches to reducing immunosuppression vary among transplant centers, and there are no randomized controlled trials that directly compare different protocols.

- Prior to reducing immunosuppression, we obtain a plasma BKPyV quantitative polymerase chain reaction (PCR) and subsequently monitor the plasma quantitative PCR every one to two weeks until BKPyV DNA is undetectable for two consecutive tests obtained at least one week apart.

- In addition, we monitor the serum creatinine level weekly.
- If the serum creatinine level increases by ≥25 percent from baseline at any time while immunosuppression is being reduced, the patient should be evaluated for the possibility of acute rejection.

- In patients who are on a triple immunosuppression therapy consisting of a calcineurin inhibitor (tacrolimus or cyclosporine), an antimetabolite (mycophenolate mofetil/sodium or azathioprine), and prednisone, we initially reduce the dose of the antimetabolite by 50 percent.
- If the BKPyV viral load does not decrease within two to four weeks, we completely discontinue the antimetabolite.

- If there is still no decrease in viral load after another two weeks, we decrease the dose of the calcineurin inhibitor by 25 to 50 percent.
- Targeting a whole blood tacrolimus trough level of 4 to 6 ng/mL or a whole blood cyclosporine trough level of 60 to 100 ng/mL.

- An alternative approach that is used by others is to 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.

- In patients who are on a glucocorticoid-free maintenance regimen with a calcineurin inhibitor and an antimetabolite without prednisone, a similar approach as described above for patients on triple immunosuppression therapy may be used.

- An alternative approach is to reduce both the calcineurin inhibitor and the mycophenolate, which allows both the targeting of two pathways and lower total immunosuppression.

- Following resolution of BKPyV viremia or biopsy-proven BKPyVAN, the decision to increase the level of maintenance immunosuppression should be individualized, taking into consideration the risk of acute rejection as well as the risk for recurrent BKPyV.

ADJUNCTIVE THERAPIES

- Several agents have been shown to have in vitro anti-BKPyV activity.
- However, we do **not** routinely use any of these agents for the treatment of BKPyV infection, given that the efficacy of these agents has not been established and use of these therapies has not been clearly shown to be superior to reduction in immunosuppression alone.

INTRAVENOUS IMMUNE GLOBULIN (IVIG)

- We do not routinely administer IVIG for the treatment of BKPyVAN.
- However, 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 (ie, immunoglobulin G [IgG] <400 mg/dL).

- We typically administer intravenous hydration with normal saline (10 to 20 mL/kg) prior to starting the infusion to mitigate the risk of acute kidney injury (AKI).
- IVIG is administered at a dose of 300 mg/kg every three weeks in conjunction with a reduction in immunosuppression.
- We repeat 21-day trough IgG levels after three months of therapy with the goal of maintaining an IgG level >400 mg/dL.

- Limited data are available concerning the efficacy of **IVIG** in patients with BKPyVAN.
- Some observational studies have reported clearance of BKPyV viremia following IVIG therapy.

LEFLUNOMIDE

- **Leflunomide** is a prodrug.
- Its active metabolite, A77 1726, has both immunosuppressive and antiviral activity.
- We do **not** use leflunomide for the treatment of BKPyV infection given its uncertain efficacy, long half-life, the potential for hematologic toxicity and hepatotoxicity, the wide interpatient A77 1726 level variability in metabolism, and the inability to easily monitor A77 1726 levels.

CIDOFOVIR

- **Cidofovir** is a nucleotide analog of cytosine that is active against various DNA viruses and is approved for both HIV-associated cytomegalovirus (CMV) retinitis and the topical treatment of genital warts.
- Cidofovir has modest in vitro activity against polyomaviruses.

- Cidofovir is potentially highly nephrotoxic, resulting in proteinuria and kidney failure in 20 percent of patients.
- This agent has caused at least one case of subacute interstitial nephritis, which led to end-stage kidney disease (ESKD).
- It should **only** be considered for treatment of BKPyVAN when other interventions have failed.

QUINOLONE ANTIBIOTICS

- We do **not** use quinolone antibiotics as an adjunctive therapy to treat BKPyV infection.
- Although quinolone antibiotics were initially reported to have anti-BKPyV activity.
- Two randomized trials showed no benefit of **levofloxacin** given either prophylactically immediately following transplantation or as treatment for active BKPyV viremia.

EXPERIMENTAL THERAPIES

- Based upon the important role of cellular and humoral immune mechanisms in control of BKPyV infection, and the absence of other proven treatments, immune-based therapies are being actively assessed in human clinical trials.

- Virus-specific T cells (VSTs) against BKPyV are being assessed for safety, tolerability, and antiviral effect in an ongoing multicenter trial of kidney transplant recipients with BKPyV viremia, based upon encouraging preliminary results of VSTs for BKPyV-associated hemorrhagic cystitis or nephropathy in hematopoietic cell transplant recipients (ClinicalTrials.gov identifier: NCT04605484).

- BKPyV-specific antibodies are being assessed for safety, tolerability, and antiviral effect in an ongoing multicenter trial of kidney transplant recipients with BKPyV viremia (ClinicalTrials.gov identifiers: NCT04294472, NCT05769582).

CONCURRENT BKPyVAN AND ACUTE REJECTION

- The coexistence of BKPyVAN and acute rejection in a kidney allograft biopsy remains controversial.

- There are no data to guide the optimal management of patients with concurrent BKPyVAN and acute rejection.
- Some experts advocate for treating the acute rejection first (eg, with pulse glucocorticoids) and then subsequently reducing immunosuppression as a second step once the patient has had a clinical response to antirejection treatment (ie, a decrease in serum creatinine level).

- By contrast, other experts avoid augmented immunosuppression and favor a reduction in maintenance immunosuppression alone.
- If immunosuppression is augmented, more frequent monitoring of BKPyV viremia may be warranted.

ACUTE REJECTION AFTER REDUCING IMMUNOSUPPRESSION

- Acute rejection can occur in 8 to 12 percent of kidney transplant recipients with BKPyV viremia or established BKPyVAN following a reduction in immunosuppression.
- Acute rejection should be suspected in patients whose serum creatinine levels increase after immunosuppression has been decreased.
- Obtaining a kidney allograft biopsy in this setting may be helpful to establish the diagnosis of rejection.

- The optimal approach to managing patients who develop acute rejection after reducing immunosuppression is not well defined and frequently varies from center to center.
- In general, we avoid augmenting immunosuppression in such patients if they have biopsy-confirmed BKPyVAN and maintain immunosuppression at the same reduced level as it was when the patient developed rejection.

KIDNEY RETRANSPLANTATION

- Retransplantation in patients with graft failure due to BK polyomavirus (BKPyV)-associated nephropathy (BKPyVAN) is a reasonable option and has been successfully performed.
- In general, the absence of BKPyV replication should be confirmed prior to retransplantation, although successful preemptive, living, related kidney transplants during active BKPyVAN with viremia have been reported.

- We do not routinely perform nephrectomy of the failed allograft or of the native kidneys, which may serve as a reservoir and a source of reinfection, as there are no high-quality data to support this approach.

BKPVVAN

IN THE NATIVE KIDNEYS

- BK polyomavirus (BKPyV) virema and BKPyV-associated nephropathy (BKPyVAN) have been reported in immunocompromised patients with native kidneys (eg, in hematopoietic stem cell transplant recipients and nonkidney solid organ transplant recipients).
- Viremia is not uncommon and may reflect the net state of immunosuppression.
- Progression to BKPyVAN is rare.


Thank You
For Your
Attention