YASHODA HOSPITALS

Simultaneous Pancreas & Kidney Transplantation

Treatment for patients with **Kidney failure** related to **Type 1 diabetes**

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Case presentation

- A 38-year-old man with end-stage renal failure (ESRF) secondary to type 1 diabetes mellitus (DM1) underwent SPKTRs

- Immunosuppression consisted guideline center :ATG induction, steroid withdrawal, and tacrolimus (FK) and mycophenolate mofetil (MMF) maintenance.

Whats your idea about Immunosuppressive therapy?

Kidney and pancreas transplantation procedures

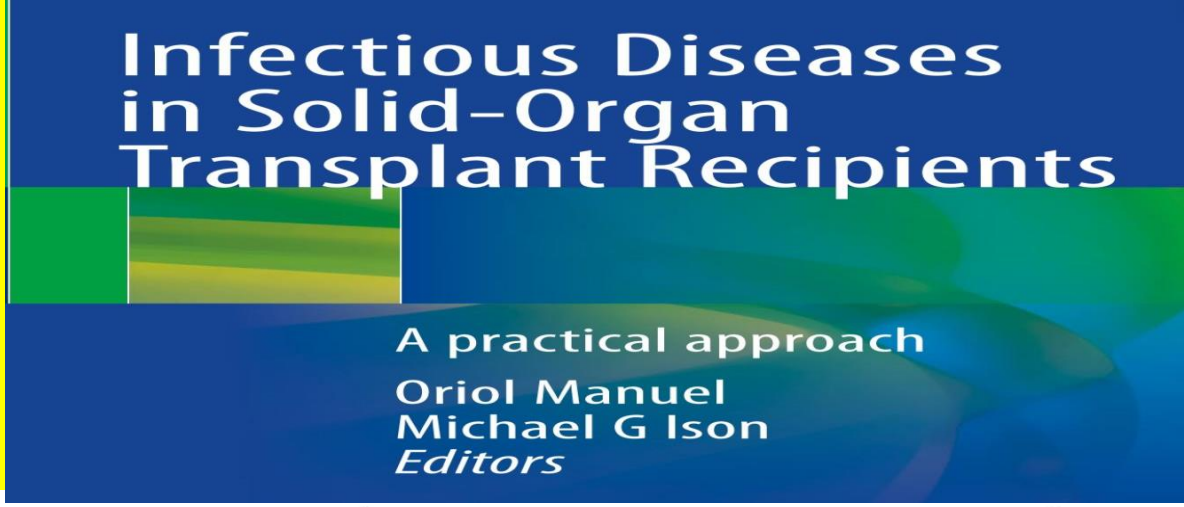
- Donor pancreata/kidneys were procured from **deceased donors** with no evidence of pancreatic or renal dysfunction. Pancreata were placed in the recipient's right iliac fossa with enteric drainage of exocrine secretions using a diverting **Roux-en-Y anastomosis** and anastomoses to the iliac vasculature. Kidneys were placed in the recipient's left iliac fossa with vascular anastomoses to the iliac vessels.

Whats your idea about prophylaxis??

prophylaxis

- All SPKTRs with lymphocyte depletion induction received a prophylaxis with valgangciclovir for 3 months posttransplantation.
- Oral prophylaxis for Pneumocystis jirovecii pneumonia with trimethoprim/sulphamethoxazole was administered at least 12 months posttransplantation.
- Systemic anti-yeast prophylaxis for 2 and 4 weeks, post-transplant.
- Screening for BKV load in serum was performed during the first posttransplant year and annually thereafter.

prophylaxis



Induction agent	Donor CMV antibody	Recipient CMV antibody	Prophylaxis	Monitoring with CMV viral load
Antithymocyte globulin	Positive	Positive	Valganciclovir × 3 months	Monitoring while on prophylaxis only if clinically indicated by symptoms; consider weekly monitoring after prophylaxis × 8–12 weeks in higher-risk patients and those on more potent immunosuppression
	Negative	Positive		
	Positive	Negative	Valganciclovir × 6 months (plus consider weekly monitoring afterward × 8–12 weeks in higher risk D+R− on more potent IS)	
	Negative	Negative	Acyclovir, famciclovir, or valacyclovir × 3 months[a]	

Quantitative PCR for BKV-DNA detection

- A 1year later the patient had deteriorating graft function& mild-moderate hydronephrosis
- Immunosuppression consisted steroid , tacrolimus (FK) and mycophenolate mofetil (MMF) maintenance.

- At the time of diagnosis the polyoma viral load was 1.3 × 109 DNA copies/mL in the urine and 1.6 ×106 DNA copies/mL in the serum.

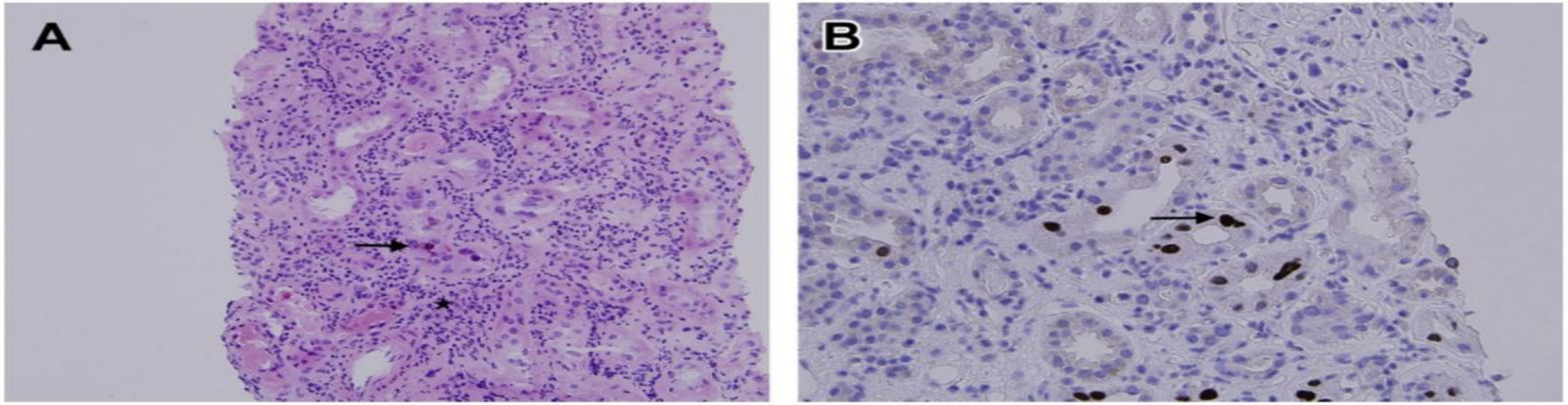
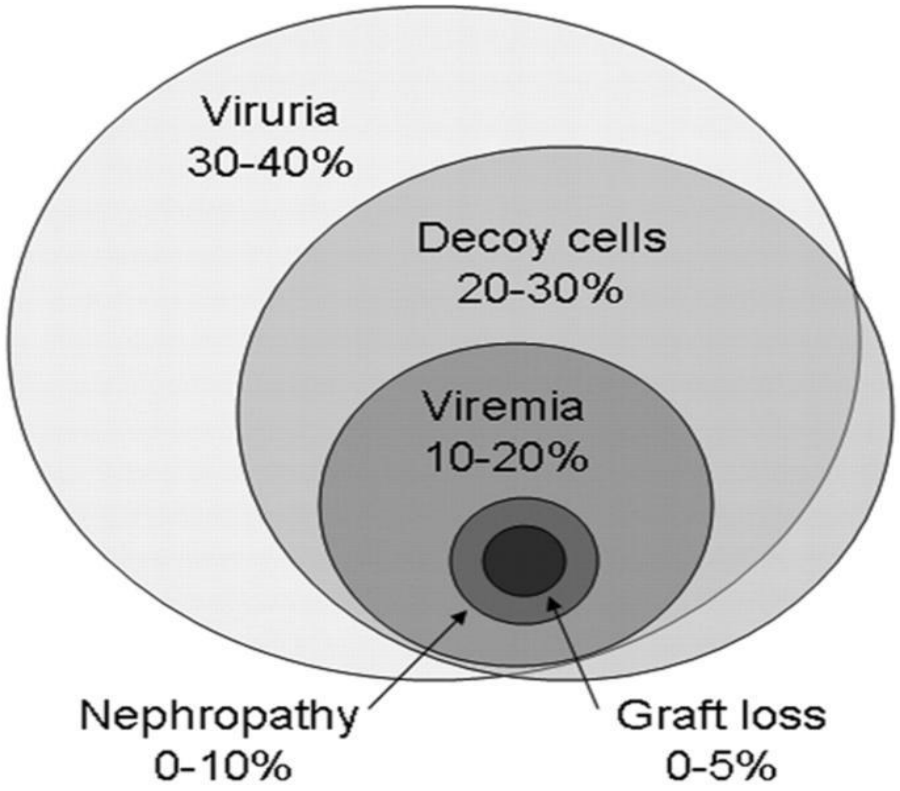


Fig. 1. (*A*) Hematoxylin-eosin (H&E) stain of renal biopsy showing positive tubular cells viral inclusions and interstitial inflammation. Tubular epithelial cells with cytopathic changes due to BK inclusions (*black arrow*). Interstitial inflammation (*black star*). (*B*) Immunohistochemical stain of renal biopsy showing positive staining for the BK T antigen. Tubular epithelial cells showing viral inclusions that are positive for simian virus 40 antigen by immunohistochemistry (*arrow*).

- The patient underwent percutaneous renal allograft biopsy, and BKVN was diagnosed.

Clinical Manifestations



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

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DIAGNOSIS

Management of BK Polyomavirus Infection in Kidney and Kidney-Pancreas Transplant Recipients

A Review Article

Nissreen Elfadawy, MS, MD[a,*], Masaaki Yamada, MD[b], Nagaraju Sarabu, MD[a]

KEYWORDS
- Kidney transplantation • BK virus • BKV-associated nephropathy (BKVAN)
- Polyomavirus

KEY POINTS
- BK virus (BKV) infection is common in kidney transplant recipients.
- BKV-associated nephropathy can cause premature graft loss in severe cases.
- Preventive strategy with active surveillance has improved outcomes of BKV infection but optimal management and specific therapy remain unclear and variable.
- Judicious immunosuppression adjustment is warranted in case of significant BK viremia and nephropathy.
- Currently, there is a limited role of use of antiviral agents either as prophylaxis or active treatment.

Table 2
Utility of BK virus screening methods

Method	Utility	Sensitivity[a]	Specificity[a]	PPV[a]	NPV[a]	Disadvantage	Advantage
1. Urine							
Decoy Cells Qualitative PCR Quantitative PCR	++ + +++	100%	45%	Low	High	• Decoy cells identification needs experience • Not to monitor decline in viral load after decrease immuno-suppression due to delayed response	• Less cost • Precedes BK viremia by 6–12 wk and flags patients who require intervention and intensive screening by plasma PCR
2. Plasma							
Qualitative PCR Quantitative PCR	+ ++++	100%	66%[b]	High	Low	• Expensive • May progress to BKVAN quickly, with a window period of only 2 wk	• High PPV • Immediate response to reduc-tion in immunosuppression

Risk factors associated with BKVN in SPKTRs

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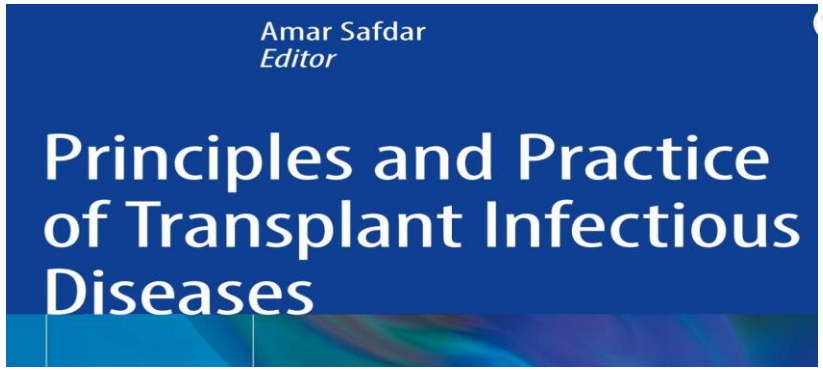
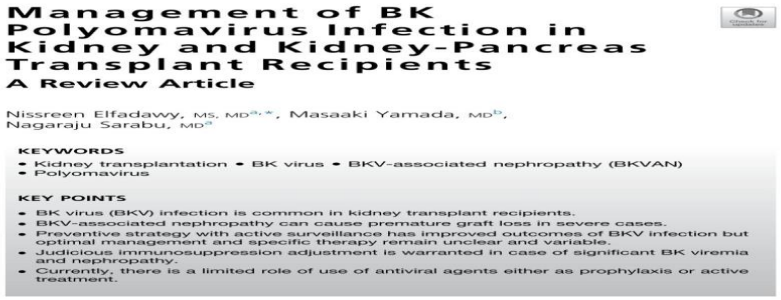
Table 1
Risk factors of BK virus reactivation and BK virus–associated nephropathy

Risk Factors of BKV Reactivation After Transplantation

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

Whats your plan??





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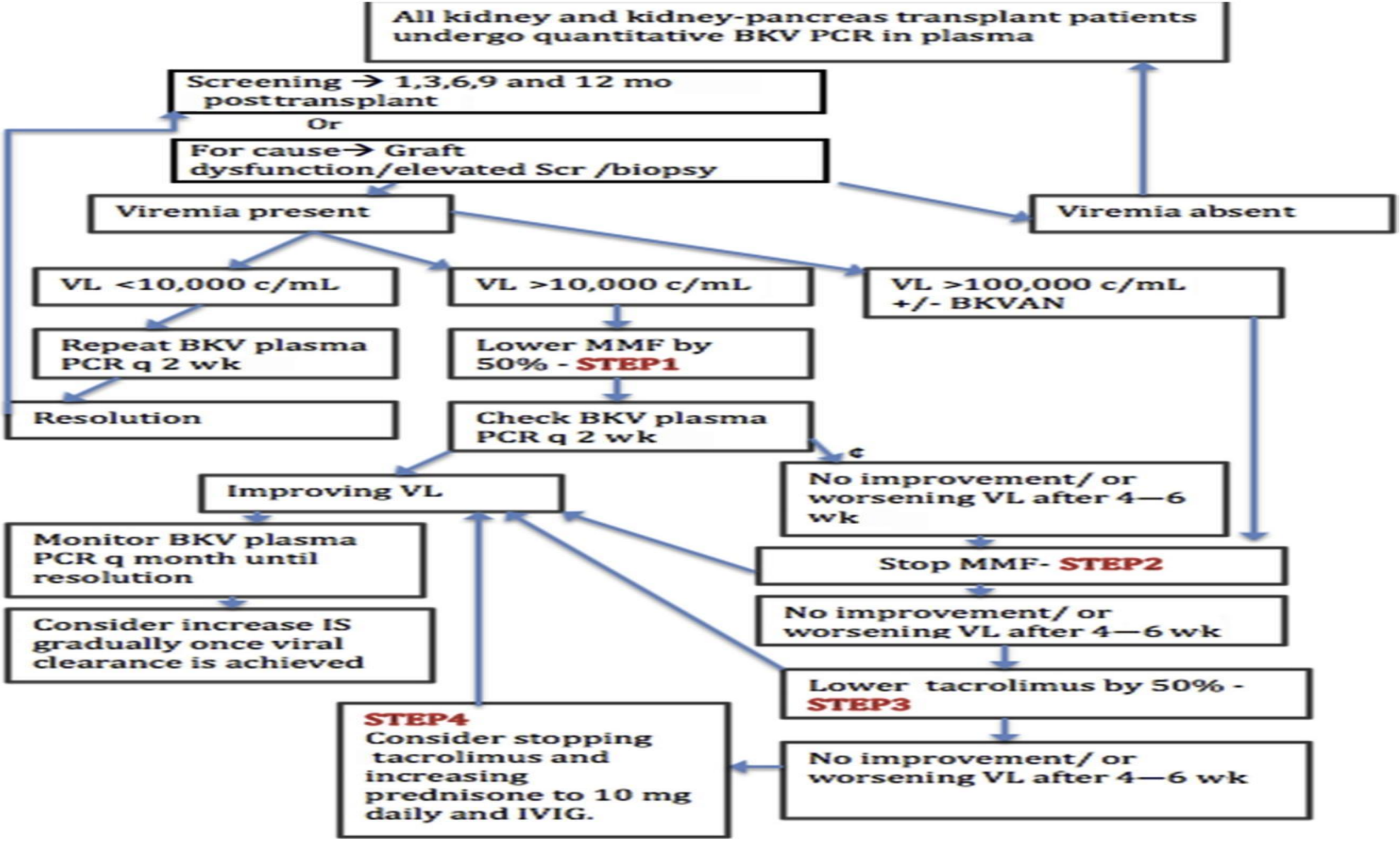
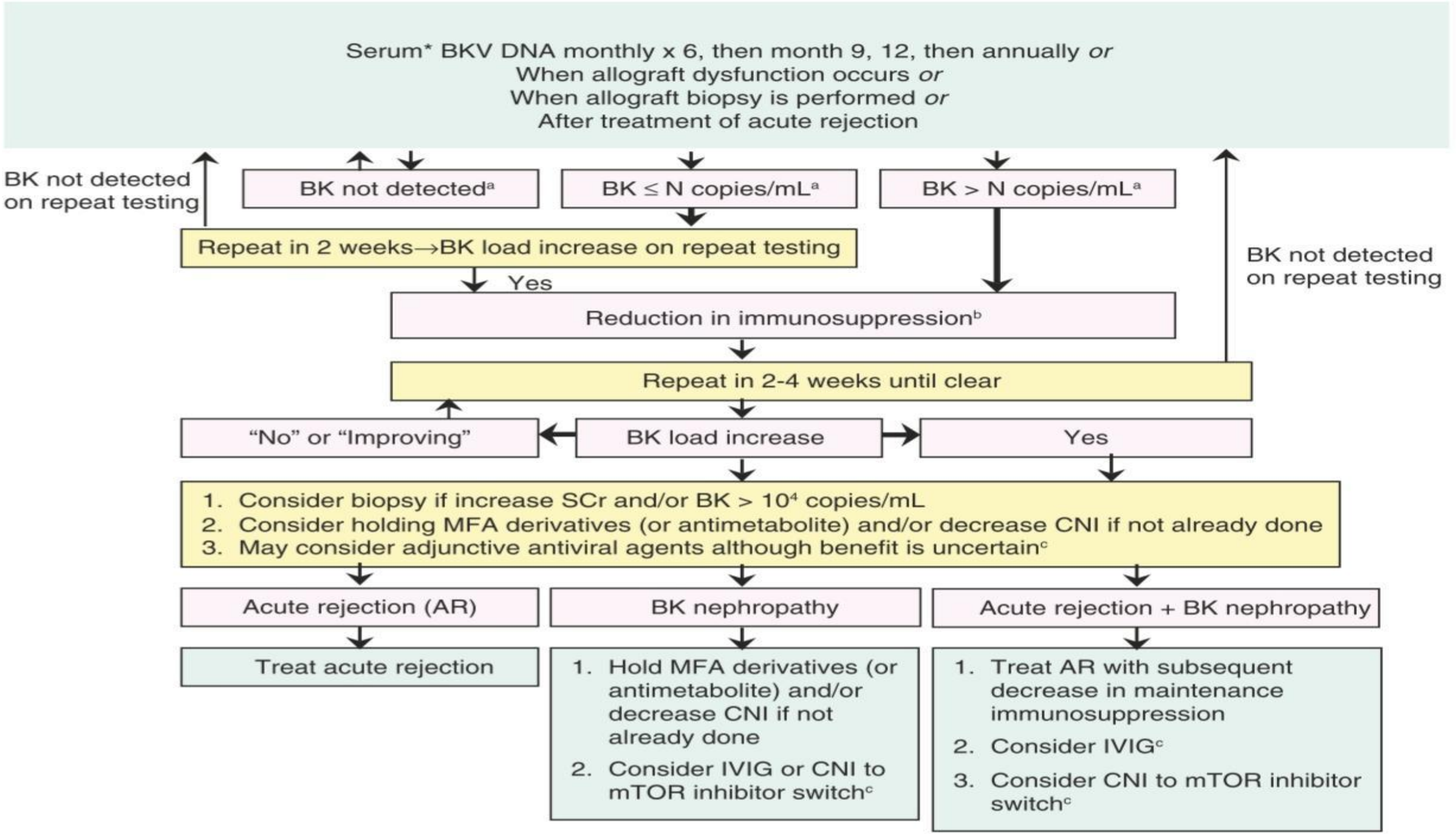

All kidney and kidney-pancreas transplant patients undergo quantitative BKV PCR in plasma
Screening → 1,3,6,9 and 12 mo posttransplant
Or
For cause→ Graft dysfunction/elevated Scr /biopsy
Viremia present
Viremia absent
VL <10,000 c/mL
VL >10,000 c/mL
VL >100,000 c/mL +/- BKVAN
Repeat BKV plasma PCR q 2 wk
Lower MMF by 50% - STEP1
Resolution
Check BKV plasma PCR q 2 wk
¢
Improving VL
No improvement/ or worsening VL after 4—6 wk
Monitor BKV plasma PCR q month until resolution
Stop MMF- STEP2
Consider increase IS gradually once viral clearance is achieved
No improvement/ or worsening VL after 4—6 wk
Lower tacrolimus by 50% - STEP3
STEP4
Consider stopping tacrolimus and increasing prednisone to 10 mg daily and IVIG.
No improvement/ or worsening VL after 4—6 wk


Serum* BKV DNA monthly x 6, then month 9, 12, then annually or
When allograft dysfunction occurs or
When allograft biopsy is performed or
After treatment of acute rejection
BK not detected on repeat testing
BK not detected[a]
BK ≤ N copies/mL[a]
BK > N copies/mL[a]
Repeat in 2 weeks→BK load increase on repeat testing
Yes
Reduction in immunosuppression[b]
BK not detected on repeat testing
Repeat in 2-4 weeks until clear
"No" or "Improving"
BK load increase
Yes
1. Consider biopsy if increase SCr and/or BK > 10⁴ copies/mL
2. Consider holding MFA derivatives (or antimetabolite) and/or decrease CNI if not already done
3. May consider adjunctive antiviral agents although benefit is uncertain[c]
Acute rejection (AR)
BK nephropathy
Acute rejection + BK nephropathy
Treat acute rejection
1. Hold MFA derivatives (or antimetabolite) and/or decrease CNI if not already done
2. Consider IVIG or CNI to mTOR inhibitor switch[c]
1. Treat AR with subsequent decrease in maintenance immunosuppression
2. Consider IVIG[c]
3. Consider CNI to mTOR inhibitor switch[c]

MANAGEMENT

- Discontinuation of MMF
- Reduce CNI then stopping CNI
- The loading dose of leflunomide is 100 mg daily for 3 to 5 days, followed by maintenance at 20 to 60 mg daily
- IVIG is 1 to 2 g/kg divided over 2 to 5 days.
- Prednosolone 10 mg

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TREATMENT

Study (year)	Study Design	Immunosuppression Adjustment Strategy	Viremia/ BKAN	BKV Clearance	Allograft Loss	Acute Rejection After BK Treatment	Mean Follow-up	Comments
Immunosuppression Reduction								
Hirsch[23] (2002)	Prospective cohort	Varied: CNI minimization or switch of agent	10/5	3/5	0/10	NR	1.6 y post-KTx	4/5 patients with BKAN also had concurrent rejection and received antirejection treatment and adjustment of IS
Ramos[44] (2002)	Retrospective cohort	15/67 no reduction; 34/67 CNI minimization; 8/67 tac → CyA; 3/67 CNI → mTORi; 36/67 MMF d/c; 14/67 MMF 50% reduction	NR/67	5/67	11/67	8/67	1 y post-BKAN	6/67 patients developed ureteral obstruction
Celik[112] (2003)	Case series	Not described; 31/66 biopsies had initial steroid treatment followed by decreased IS, 6/66 no change in IS, 29/66 decreased IS from outset	NR/31	11/45 biopsies at 8 wk; 15/21 biopsies after 8 wk	11/31	NR	NR	No long-term difference was seen with initial treatment with steroids or IS reduction from outset
Brennan[50] (2005)	Prospective cohort	Discontinuation of antiproliferative agent (AZA or MMF); if viremia did not clear after 4 wk, CNI dose was reduced (target CyA 100-200 ng/mL, Tac 3-5 ng/mL)	23/0	22/23	0/23	2/23	1 y post-KTx	Patients randomly assigned to Tac or CyA before BK diagnosis; no difference in incidence between groups and no significant differences in patient survival or allograft loss

								patient survival or allograft loss
Saad[113] (2008)	Case series	50% reduction of MMF, CNI, and/or mTORi	24/16	24/24	1/24	3/24	3.6 y post-KTx; 2.6 y post-BK	71% had stable or improved kidney function; 29% had kidney function decline; the single allograft failure was due to BKAN recurrence during pregnancy
Almeras[114] (2008)	Prospective cohort	Viremia: 25% reduction in CNI and 50% reduction in MMF; BKAN: 25% reduction in CNI and discontinuation of MMF	13/3	8/11 viremic w/o BKAN patients; 1/3 BKAN patients	0/13	3/13	1 y post-KTx	
Weiss[115] (2008)	Case series	BKAN: Withdrawal group (n = 17) d/c either antiproliferative (20%) or CNI (80%); Reduction group (n = 18) Tac 3-6 ng/mL, CyA 75-150 ng/mL, MMF 500 BID, sirolimus 2 mg/d (goal < 8 ng/mL); Viremia w/o BKAN: withdrawal of CNI (n = 2), IS reduction (n = 28)	65/35	NR	BKAN 16/35; viremia w/o BKAN 0/30	2/35	Up to 5 y	65% of patients were on CNI/mTOR regimen before BKAN diagnosis; antiviral therapy used in many patien cidofovir (n = 7), IVIG (n = 16), leflunomide (n = 9); 1 y allograft survival: 87.8% in withdrawal group vs 56.2% in reduction group ($P = 0.03$). HR of IS withdrawal, 0.28 (95% CI, 0.08-0.93; $P = 0.04$)
Schaub[68] (2010)	Prospective cohort	Sustained viremia: CNI minimization followed by MMF dose reduction if viremia persisted	38/13	35/38	0/38	10/35 patients who cleared viremia	2.9 y post-KTx	7/38 (18%) patients had concurrent treatment for rejection: 1 with rituximab and IVIG, 6 with steroid pulses

Study (year)	Study Design	Immunosuppression Adjustment Strategy	Viremia/ BKAN	BKV Clearance	Allograft Loss	Acute Rejection After BK Treatment	Mean Follow-up	Comments
Hardinger[116] (2010)	Retrospective cohort	Discontinuation of antiproliferative agent (AZA or MMF); if viremia did not clear after 4 wk CNI dose was reduced (target CyA 100-200 ng/mL, Tac 3-5 ng/mL)	23/0	22/23	4/23; 1/23 DCGL	5/23	5 y post-KTx	5 y follow-up of study by Brennan et al[50]
Sawinski[111] (2015)	Retrospective cohort	Discontinuation of antiproliferative agent (MMF or AZA); if viremia did not clear, CNI was reduced; if viremia did not clear Tac was switched to CyA	132/12	NR	8/132	NR	3 y post-KTx	Class II DSA development was more common in patients with persistent BK viremia than that in patients with no viremia (OR, 2.53; 95% CI, 1.40-4.59); BK viremia was not associated with allograft loss (HR, 0.80; 95% CI, 0.37-1.73)
Seifert[117] (2017)	Retrospective cohort	Discontinuation of antiproliferative agent (AZA or MMF); if viremia did not clear after 4 wk CNI dose was reduced (target CyA 100-200 ng/mL, Tac 3-5 ng/mL)	20/0	19/20	7/20; 1/20 DCGL	NR	10 y post-KTx	10 y follow-up of study by Brennan et al[50]; 4/20 patients with BK viremia developed rejection, but the timing in respect to viremia (before or after) was not reported
Bischof[118] (2018)	Retrospective cohort	Sustained viremia: CNI minimization followed by MMF dose reduction if viremia persisted	105/33	101/105	Viremia: 6/105; BKAN: 2/33; 1/33 DCGL	11/101	6.6 y post-KTx; 5 y post-BK viremia	24 viremic patients had low-level viremia (<10,000 copies/mL); 12/101 who cleared viremia had relapse in viremia; 12/105 had concurrent rejection. 6 of them were treated with increased IS; 5/33 allograft loss due to rejection

Baek[119] (2018)	Retrospective cohort	Not described: minimization or discontinuation or CNI or antiproliferative	79/12	61/79	NR	17/79	6 y post-KTx	MMF discontinuation vs reduction was protective for acute rejection (OR, 0.11; 95% CI, 0.02-0.61); CNI level reduction ≥ 20% associated with acute rejection (OR, 33.75; 95% CI, 4.26-267.25)
LFN								
Josephson[100] (2006)	Case series	LFN alone (n = 19) or LFN + cidofovir (n = 7) coupled with IS reduction (d/c MMF, Tac through target 4-6 ng/mL). LFN dose: LD 100 mg/d ×5 d, MD 20-60 mg/d; target blood level 50-100 μg/mL	26/26	11/26	4/26	NR	0.5-3.3 y post-KTx	All patients were treated with IS reduction before starting antiviral therapy; there were kidney-pancreas recipients (n = 7), heart-kidney-pancreas recipient (n = 1), and kidney recipients (n = 18)
Faguer[101] (2007)	Case series	MMF replaced by LFN (LD 100 mg/d ×5 d, MD 40 mg/d, target levels 40-80 mg/L), and Tac decreased to target level of 6-10 ng/mL	8/12	5/12	2/12	1/12	1.3 y post-KTx	3 patients had concurrent acute cellular rejection treated with steroid pulses

Study (year)	Study Design	Immunosuppression Adjustment Strategy	Viremia/ BKAN	BKV Clearance	Allograft Loss	Rejection After BK Treatment	Mean Follow-up	Comments
Basse[103] (2007)	Case series	BK viremia (n = 1): MMF halved; BKAN + rejection (n = 4): steroid pulses, MMF replaced by LFN (target level 40-100 mg/L)	7/4	NR	0/7	NR	1.2-2 y post-KTx	All 4 cases of BKAN had concurrent allograft rejection on kidney biopsy
Leca[104] (2008)	Case series	MMF replaced by LFN (LD 60 mg/d ×3 d, MD 20 mg/d) and Tac level decreased to 5 ng/mL; 2 groups based on LFN levels: "low level" <40 μg/mL (n = 12) and "high level" >40 μg/mL (n = 9)	21/21	11/21; low level 6/12; high level 5/9	4/21; low level 3/12; high level 1/9	2/21; low level 0/12; high level 2/9	1.1 y -KTx	8 patients also received cidofovir, and 3 patients received IVIG; 2 patients developed TMA after leflunomide treatment
Teschner[105] (2009)	Case series	MMF replaced with LFN (LD 100 mg/d ×3 d, MD 20 mg/d, target level 40 μg/mL) + Tac level decreased to 4-6 ng/mL	13/13	11/13	1/13	0/13	2 y post-KTx; 1.3 y post-BKAN	
Krisl[102] (2012)	Retrospective cohort	MMF replaced by LFN, CNI minimization (LFN group, n = 52); MMF minimization or d/c, CNI minimization (CNT group, n = 24)	76/33; LFN 52/32; CNT 24/1	LFN 16/52; CNT 15/24; viremia: LFN 8/20; CNT 15/23	LFN 8/52; CNT 2/24	LFN 10/52; CNT 2/24; viremia: LFN 2/20; CNT 0/23	1.1-1.4 y post-BKAN	In multivariate analysis, leflunomide use was not associated with BK viral clearance (OR, 1.10; 95% CI, 0.19-6.5; $P = 0.92$); 9 patients also received cidofovir

Cidofovir								
Tong[120] (2004)	Case series	IS reduction alone (n = 2); IS reduction + cidofovir (0.25 mg/kg q4d; n = 5)	7/7	5/7	0/7	NR	1.5 y post-BKAN	
Kuypers[99] (2005)	Retrospective cohort	IS reduction + cidofovir (0.5-1 mg/kg qw) (n = 8); IS reduction alone (n = 13)	21/21	Cidofovir 6/8; no cidofovir 6/13	Cidofovir 0/8; no cidofovir 9/13	NR	2 y post-BKAN	2 patients in the cidofovir group had concurrent rejection and were treated with steroids
Wadei[110] (2006)	Case series	IS reduction (either decrease overall IS, or switch to CyA-based regimen; n = 23); IS reduction + cidofovir (0.25 mg/kg q2w ×4, if BKAN persisted 0.5 mg/kg q2w ×4-5) (n = 20); IS reduction + cidofovir + IVIG (2.5 g/kg; n = 10); IS reduction + IVIG (n = 2)	31/55	NR	8/55	9/55; 6/30 in cidofovir treated; 3/25 without cidofovir	1.6 post-BKAN	Neither cidofovir, IVIG. nor CyA conversion was associated with improved allograft functional outcome or BKV clearance in kidney tissue; allograft loss was not reported for each specific treatment group
Kuypers[121] (2008)	Prospective cohort	IS reduction + cidofovir (0.5-1 mg/kg qw; n = 26); IS reduction alone (n = 15)	41/41	Cidofovir 15/26; no cidofovir 7/15	Cidofovir 4/26; no cidofovir 11/15	Cidofovir 4/26; no cidofovir 1/15	2.5 y post-BKAN	Allograft survival was better in the cidofovir group ($P = 0.0002$), but no difference in BK viral clearance ($P = 0.44$); 3 patients treated with cidofovir developed severe anterior uveitis

Study (year)	Study Design	Immunosuppression Adjustment Strategy	Viremia/ BKAN	BKV Clearance	Allograft Loss	Acute Rejection After BK Treatment	Mean Follow-up	Comments
Fluoroquinolones								
Lee[106] (2014)	Prospective, double-blind, placebo-controlled, randomized trial	IS reduction + levofloxacin (30-d course; n = 20); IS reduction alone (n = 19)	39/0	Levofloxacin 8/20; control 6/19	Levofloxacin 0/20; control 2/19	Levofloxacin 1/20; control 0/19	0.5 y postviremia	Reduction of BK viral load was similar at 3 and 6 mo in both groups; leflunomide was also used in 6 patients
mTORi								
Wali[122] (2004)	Case series	50% reduction in IS followed 12 wk after by d/c of Tac and MMF, and starting sirolimus (target level 10-12 ng/mL)	3/3	3/3	0/3	0/3	1.5 y post-BKAN	
Jacobi[98] (2013)	Retrospective cohort	Low viremia (10^3-10^4 copies/mL): reduction CNI by 30% and MMF by 50% (n = 15). If viremia persists, change to sirolimus (target 5-8 ng/mL) + low CyA (target 60-80 ng/mL) regimen (n = 7), or other regimens (n = 4); high viremia (>10^4 copies/mL) or BKAN: change to sirolimus (target 5-8 ng/mL) + low CyA (target 60-80 ng/mL) regimen (n = 13), or other regimens (n = 2), or reduction in IS (n = 7)	48/22	43/48	5/48	3/48	1.8 y post-KTx	Overall viral replication did not differ between different treatment groups of patients with either BK viremia or BKAN

IVIG								
Sener[107] (2006)	Case series	50% reduction in IS + IVIG (2 g/kg)	7/8	4/8	1/8	1/5	1.25 y post-BKAN	2 patients were initially misdiagnosed as having ACR
Vu[109] (2015)	Retrospective cohort	MMF replaced by LFN (40 mg/d), if persistent after 4 wk CNI was decreased (CyA target 100-200 ng/mL or Tac 3-5 ng/mL; n = 23), if persistent after 4 wk IVIG (1 g/kg) was given (n = 30)	53/10	23/53 with IS reduction only; 27/30 with IVIG	1/30	1/30	1.5 y post-BKAN	
Kable[108] (2017)	Retrospective cohort	MAT (Tac reduction or conversion to CyA + MMF reduction or conversion to LFN or AZA + ciprofloxacin 500 mg/d ×30 d + cidofovir 0.5 mg/kg q2w ×10 wk) + IVIG 100 mg/kg qw ×10 wk (n = 22); MAT alone (n = 28)	50/50	MAT + IVIG 18/22; MAT 16/28	DCGL 21/50; MAT + IVIG 6/22 MAT 15/28	MAT + IVIG 14/22; MAT 16/28	5 y post-KTx	In multivariate analysis, IVIG was associated with more effective clearance of viremia (HR, 6.82; 95% CI, 1.03-45.11; $P = 0.046$); salvage IVIG was used in 7 patients after multidimensional antiviral therapy failed

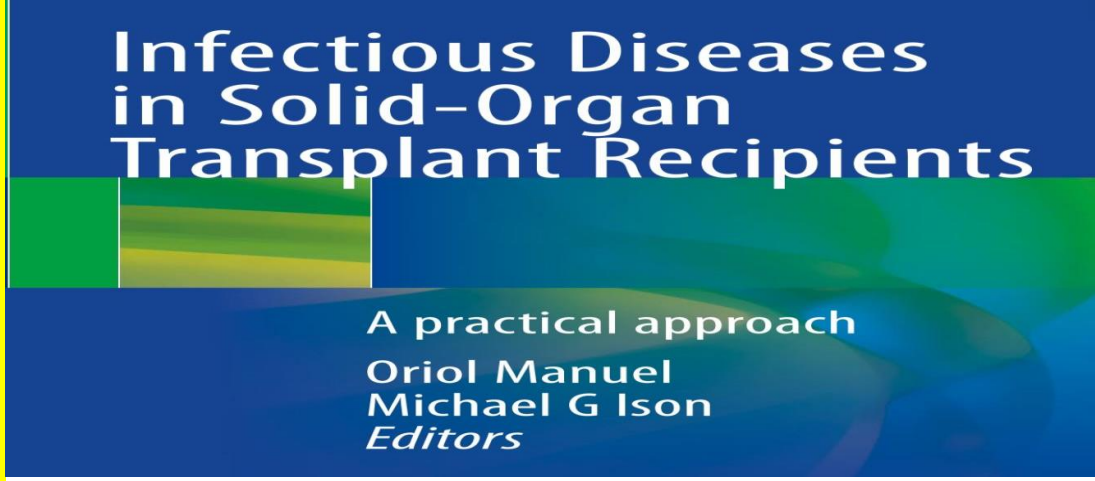
Case presentation

- Polyoma viremia responded well to immunosuppression reduction and use of another drug , but the renal allograft function continued to deteriorate.
- Approximately 2years after the initial transplantation, the patient was back on dialysis.
- His polyoma viral load remained undetectable from the time of listing to the time of retransplantation.

Retransplantation after BK Virus–Associated Nephropathy Graft Loss

- Retransplantation is recommended after BK viremia clearance to decrease risk of BKVAN in the retransplanted kidney.
- Nephrectomy of prior failed allograft if BK viremia persists despite minimization of immunosuppression remains controversial with no supporting evidence.
- The key to successful retransplantation is balance of overall immunosuppression, risk of BKV replication, and risk of rejection

Outcomes in SPKTRs with BKVN



- More severe course of BKVNin SPKTRs compared with that in KTRs
- With higher peak BKV loads
- Need for more intense therapeutic intervention
- less likely recovery to baseline serum creatinine

Outcomes in SPKTRs with BKVN

- Suggest a predominantly late-onset ofBKVN in SPKTRs compared with an early-onset of BKVN in KTRs.

- The use of lymphocyte-depleting induction has been associated with an increased incidence of BKV replication most likely due to an elimination of protective BKV-specific cellular immunity .

- Pre-existing diabetes itself has been suggested to be a possible risk factor for BKVN and at least in part explain the increased incidence of BKVN in SPKTRs

Outcomes in SPKTRs with BKVN

- This finding can be attributed to the late-onset ofBKVN with delayed diagnosis and a more pronounced injury of the allograft kidney due to BKVN

- **Fear of pancreatic allograft rejection** may in addition contribute to inadequate treatment of BKVN in SPKTRs that can lead to a more severe and prolonged course ofBKVN.

Take home message

- Reduction of immunosuppression is the mainstay of treatment of persistent BK viremia and/or biopsy-proven BKVAN

Take home message

- Previous work in SPKTRs suggested that reducing immunosuppression in an attempt to salvage the kidney allograft did not result in subsequent pancreas allograft rejection or dysfunction

Thank You!