Taiwanese Expert Consensus on Screening and Management of BK Virus Infection after Kidney Transplantation

Advisroy Board

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TABLE OF CONTENTS

LIST OF FIGURES AND TABLES

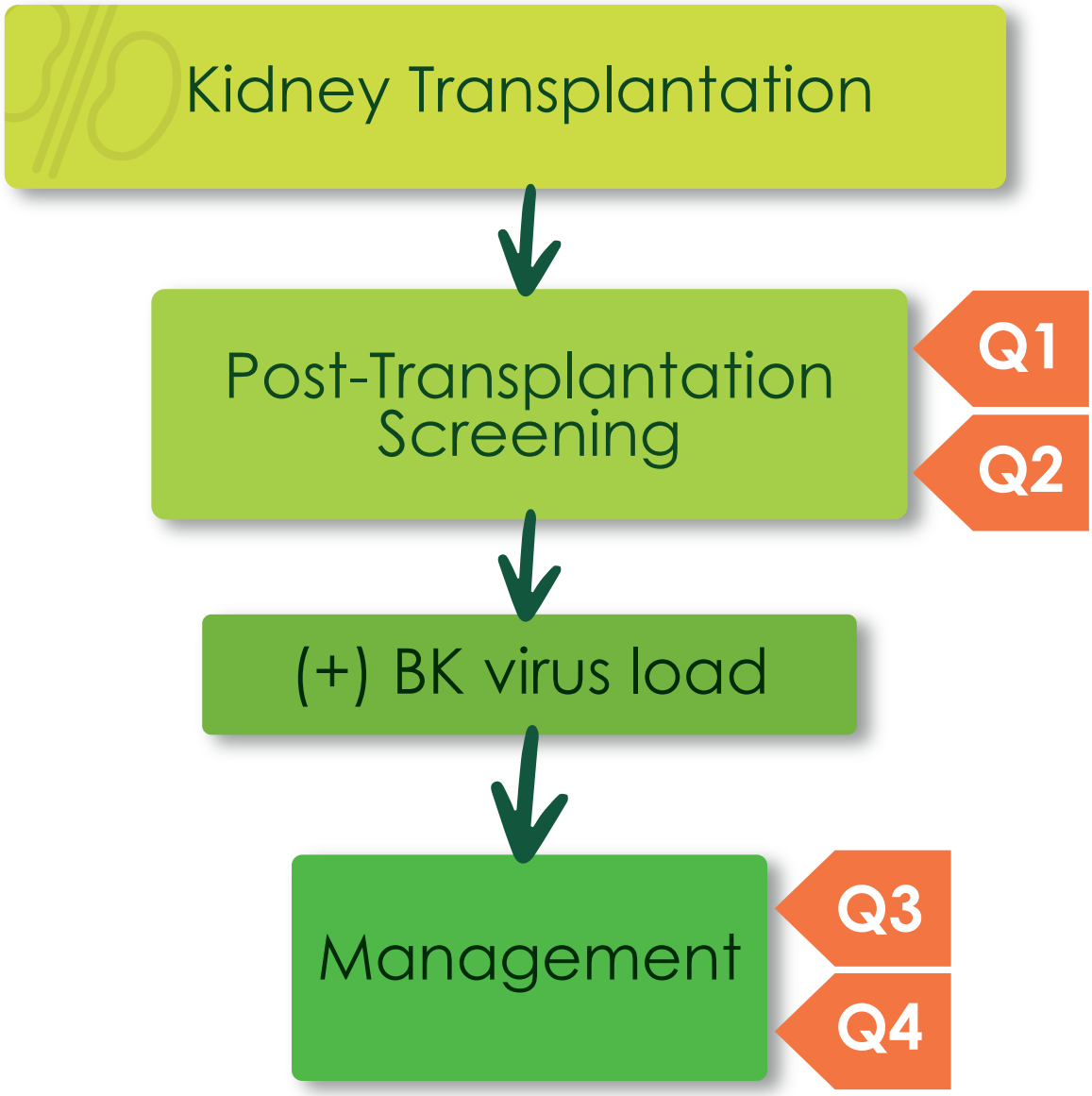
PREFACE

Human BK virus, remains a crucial cause for allograft loss among kidney transplant recipients. The incidence of BK Virus-associated nephropathy (BKVAN) is about 1-7% of kidney transplant recipients in the first year post-transplantation, among which approximately 40-60% develop progressive graft loss if there is no appropriate treatment.[1] Early diagnosis and management of BKVAN usually leads to better allograft survival than delayed diagnosis.[2] Reduction of immunosuppression is the mainstay treatment for significant BK virus replication, including probable BKVAN, presumptive BKVAN, or proven BKVAN according to biopsy results.[3] However, the optimal screening strategy and approach of BK virus infection after kidney transplantation have not been determined, and protocols vary among transplant centers and international guidelines (Appendix 1, Appendix 2).[4-6]

Given the lack of consensus guidelines, expert meetings in kidney transplantation were convened twice by The Transplantation Society of Taiwan at Sheraton Grand Taipei Hotel on October 2nd and 23rd.

The meetings were focused on discussing post-transplant BK virus screening modality and frequency/timing and management of BK viruria/viremia and BKVAN. The experts reviewed the current literature and presented the data to the attendees followed by discussion and debate. A four question-survey (Q1 and Q2 for screening; Q3 and Q4 for management) was developed and peer reviewed (Figure 1). Each question was then voted using a digital system. This booklet summarized the findings of meeting and the consensus opinion of the expert group.

Figure 1. Four questions designed for screening and management of BK virus infection in kidney transplant recipients.



TOPIC 1 SCREENING

Regular screening for BK viruria and viremia is important for early diagnosis and prevention of BKVAN.

- BK virus screening modality

Key statement

Regular screening for BK Virus infection is necessary after renal transplantation and the modality varies among the institutes. Most Experts suggest to use both urine and blood polymerase chain reaction (PCR) as screening modality, either simultaneously or urine first.

Voting results

Q1-1: What is the BK virus screening modality in your institute?

Currently, blood PCR (32%) and simultaneous blood and urine PCR (26%) are the two most used screening modality to monitor BK virus infection (Table 1). When the results were categorized by institutes, similarly, blood PCR was the most used screening modality (5 institutes), followed by urine PCR followed by blood PCR (4 institutes), and blood and urine PCR simultaneously (2 institutes) (Table 2).

Q1-2: What is your "preferred" modality of BK virus screening modality?

On the ideal side, the two most preferred screening modality are blood and urine PCR simultaneously (53%) and urine PCR followed by blood PCR (32%). Therefore, 84% of experts preferred to use both urine and blood PCR as screening modality, either simultaneously or urine first (Table 1). Table 3 showed the ideal screening modality among the experts, which is very different from the reality shown in Table 2.

Table 1. Voting results for screening modality and frequency/timing of BK virus infection in kidney transplant recipients

BK virus screening modality	Voting results (%, n/N)
Q1-1. What is the BK virus screening modality in your institute?	
• Urine cytology for Decoy cells	16 (3/19)
• Urine PCR	5 (1/19)
• Blood PCR	32 (6/19)
• Urine & blood PCR (simultaneously)	26 (5/19)
• Urine PCR followed by blood PCR	21 (4/19)
Q1-2. What is your "preferred" modality of BK virus screening modality?	
• Urine cytology for Decoy cells	0
• Urine PCR	11 (2/19)
• Blood PCR	5 (1/19)
• Urine & blood PCR (simultaneously)	53 (10/19)
• Urine PCR followed by blood PCR	32 (6/19)
BK virus screening frequency / timing	
Q2-1. What is your "current" BK virus screening frequency/timing in your institute in the 1st year after kidney transplantation?	
• Monthly in the first 3 months, followed by every 3 months	16 (3/19)
• Monthly in the first 6 months, followed by every 3 months	21 (4/19)
• Monthly in the first 9 months, then at the 12th month	0
• The 1st, 3rd, 6th,9th and 12th month	32 (6/19)
• Every 3 months	32 (6/19)
Q2-2. What is your optimal BK virus screening frequency/timing in the 1st year after kidney transplantation?	
• Monthly in the first 3 months, followed by every 3 months	21 (4/19)
• Monthly in the first 6 months, followed by every 3 months	37 (7/19)
• Monthly in the first 9 months, then at the 12th month	0
• The 1st, 3rd, 6th,9th and 12th month	37 (7/19)
• Every 3 months	5(1/19)

Abbreviations: PCR, polymerase chain reaction

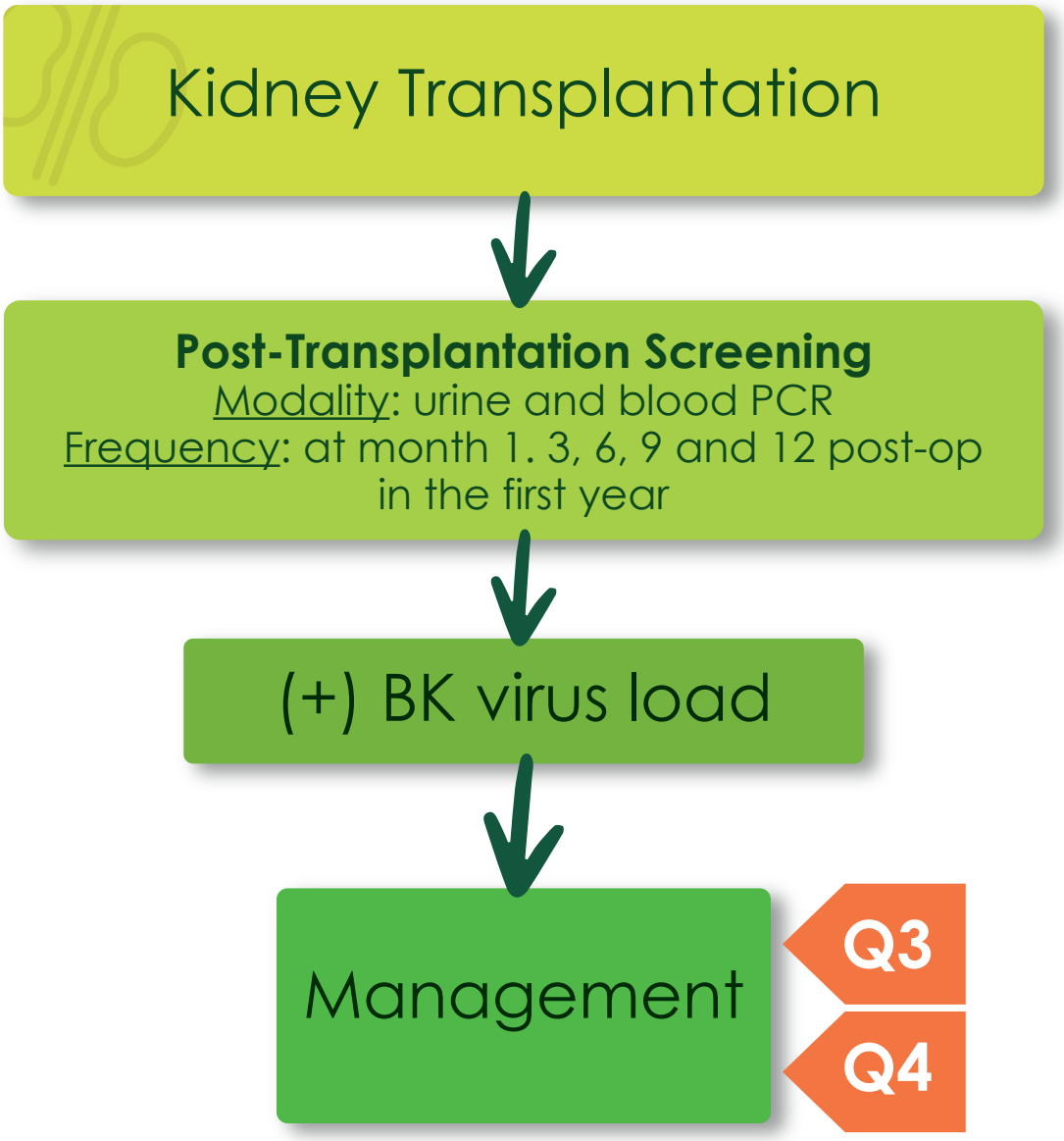
Comments

Urine PCR and blood PCR are recommended for monitoring BK virus infection after kidney transplantation (Figure 2). Urine PCR is a good early indicator for BK virus infection before blood PCR turning positive. In BKVAN screening, quantification of viral load in urine is superior to that in plasma in several ways. The appearance of BK virus in urine is earlier than that in blood during the development of BKVAN. A negative test result for urinary BK virus DNA has a high negative predictive value. BK viruria may have a wide window period of 6–12 weeks before the onset of viremia and BKVAN. Therefore, quantification of urinary BK viral load could be more appropriate to assess the risk of BKVAN at an earlier stage.[7,8]

Typically, BK viral load in urine is high and that in blood is low in the same PCR run. Usually, no BK viremia will be detected when urine viral load is less than 7.0 log10 copies/ml.[9] Although BK viremia is highly correlated with BKVAN, the alteration of urine viral load could be more significant than that of blood viral load[7,10]. Therefore, the definition of BK viremia which varies among transplant centers and international guidelines is important (Appendix 3).

Gene mutation in BK virus is very common[11,12] and may result in underestimation of BK virus infection due to the inability of primers to anneal to BK virus DNA. Therefore, the methods used for BK virus quantification need to be frequently evaluated and corrected accordingly. It may happen that quantification of urine viral load is not high with primers designed from the region of SV40 large T-antigen gene of BK virus, but is increasingly high with those designed from VP1 gene. Therefore, discovery of more primer binding sites or non-mutant consensus sites may be required for BK virus quantification.

Figure 2 . Proposed algorithm for the screening of BK virus infection in kidney transplant recipients. Abbreviations: PCR, polymerase chain reaction.



- BK virus screening frequency/timing

Key statement

All experts recommend screening for BK virus infection at month 1, 3, 6, 9 and 12 in the first year after kidney transplantation.

Voting results

Q2-1: What is your "current" BK virus screening frequency/timing in your institute in the 1st year post kidney transplant?

Currently, BK virus screening at month 1, 3, 6, 9 and 12 (32%) and every 3 months (32%) of the 1st year after kidney transplantation were the two most common options (Table 1). When the results were categorized by institutes, BK virus screening was performed every 3 months in five institutes, in the 1st, 3rd, 6th, 9th and 12th month in four institutes, monthly in the first 6 months, followed by every 3 months in four institutes, and monthly in the first 3 months, followed by every 3 months in 3 institutes (Table 2).

Q2-2: What is your "optimal" BK virus screening frequency/timing in the 1st year after kidney transplantation?

On the ideal side, most experts considered that it was optimal to conduct BK virus screening at the 1st, 3rd, 6th, 9th and 12th month (37%) or monthly in the first 6 months, followed by every 3 months (37%) in the first year after kidney transplantation. Another 21% of experts considered that the optimal screening frequency was monthly in the first 3 months, followed by every 3 months. Only 5% of experts considered that screening every 3 months was proper. In summary, 100% experts suggested screening for BK virus infection every 3 months in the first year after kidney transplantation (Table 1). Table 3 showed the ideal screening frequency among the experts, which is higher on average than screening frequency in reality shown in Table 2.

Comments

Regular screening for BK virus infection is recommended (Figure 2). It is important that screening is not just for the implementation of interventions.

Another advantage of screening is that if a test result is negative, physicians and patients will feel at ease. If it is positive, continue close monitoring is very important to support the clinical decision making. Most BKVAN occurs in the first 2 years after kidney transplantation.[13] The screening algorithm is most frequent early after renal transplantation, with lowering frequency as patients are out from kidney transplantation for a longer period of time.[14] It was reported that 26.7% of kidney transplant recipients were positive for BK viruria which was mainly detected at 3–6 months after kidney transplantation.[15] Another study also reported that the positive rate for BK viruria was high (33%) during the first 6 months after kidney transplantation, and then decreased gradually.[16] The onset of BK viruria alone was reported to be a median of 65 (27-167) days and a median of peak urine BK viral load was 123 (74-227) days after kidney transplantation.[17] The screening frequency and timing should reflect the reported data and balance the screening cost with the potential for the prevention of BKVAN.[14] More frequent monitoring depends on the relevant risk factors of BK virus infection, routine hospital practice and whether BK virus infection is detected.

However, BKVAN should be considered not only in the first year after kidney transplantation. Indeed, some patients developed BKVAN was beyond two years after kidney transplantation.[3] Late-onset BKVAN, defined as first diagnosis after the first year kidney transplantation, accounted for 14.6% of cases among kidney transplant recipients.[18]

Severe tubule-interstitial damage was very common finding in the allograft biopsy of late stage BKVAN.[19] Specially, renal fibrosis is not suitable for the replication of BK virus. Therefore, urinary BK viral load may be relative lower in patients with BKVAN and severe allograft dysfunction. It is the reason for the false-negative detection of BK virus infection by urine PCR in patients with late stage of BKVAN. All of the evidence supports the necessity of early diagnosis of BKVAN by the regular screening of BK virus infection after kidney transplantation.

Table 2. Current BK virus screening modality and frequency/timing in the 1st year post kidney transplant among experts

Expert no.	Modality			Month											
	BP	UP	UC	1	2	3	4	5	6	7	8	9	10	11	12
1	✔[a]	✔[a]		●	●	●	●	●	●			●			●
2	✔[b]	✔[b]		●	●	●	●	●	●			●			●
3	✔			●	●	●	●	●	●			●			●
4	✔[b]	✔[b]		●	●	●	●	●	●			●			●
5	✔[a]	✔[a]		●	●	●			●			●			●
6	✔			●	●	●			●			●			●
7			✔	●	●	●			●			●			●
8	✔[a]	✔[a]		●		●			●			●			●
9	✔[a]	✔[a]		●		●			●			●			●
10	✔[a]	✔[a]		●		●			●			●			●
11	✔[b]	✔[b]		●		●			●			●			●
12	✔			●		●			●			●			●
13	✔			●		●			●			●			●
14	✔					●			●			●			●
15	✔[b]	✔[b]				●			●			●			●
16		✔				●			●			●			●
17			✔			●			●			●			●
18			✔			●			●			●			●
19	✔					●			●			●			●

Each row represented an expert's answer, and was classified according to screening frequency.
[a] Urine & blood PCR (simultaneously); [b] Urine PCR followed by blood/plasma PCR.
Abbreviations : BP, blood PCR; UP, urine PCR; UC, urine cytology; PCR, polymerase chain reaction.

Table 3. Ideal BK virus screening modality and frequency/timing in the 1st year post kidney transplant among experts

Expert no.	Modality			Month											
	BP	UP	UC	1	2	3	4	5	6	7	8	9	10	11	12
1	✔[a]	✔[a]		●	●	●	●	●	●			●			●
8	✔[b]	✔[b]		●	●	●	●	●	●			●			●
12	✔[b]	✔[b]		●	●	●	●	●	●			●			●
3	✔[b]	✔[b]		●	●	●	●	●	●			●			●
17		✔		●	●	●	●	●	●			●			●
13	✔[a]	✔[a]		●	●	●	●	●	●			●			●
4	✔[a]	✔[a]		●	●	●	●	●	●			●			●
5	✔[a]	✔[a]		●	●	●			●			●			●
9	✔[a]	✔[a]		●	●	●			●			●			●
2	✔[b]	✔[b]		●	●	●			●			●			●
6	✔[a]	✔[a]		●	●	●			●			●			●
10	✔[a]	✔[a]		●		●			●			●			●
11	✔[a]	✔[a]		●		●			●			●			●
7	✔[a]	✔[a]		●		●			●			●			●
14	✔[a]	✔[a]		●		●			●			●			●
15	✔[b]	✔[b]		●		●			●			●			●
18	✔			●		●			●			●			●
19	✔[b]	✔[b]		●		●			●			●			●
16		✔				●			●			●			●

Each row represented an expert's answer, and was classified according to screening frequency.
[a] Urine & blood/plasma PCR (simultaneously); [b] Urine PCR followed by blood PCR.
Abbreviations : BP, blood PCR; UP, urine PCR; UC, urine cytology; PCR, polymerase chain reaction.

TOPIC 2 MANAGEMENT

Management of BK virus infection should depend on viral load and renal function. Adjustment of Immunosuppressive drugs could be effective for viral clearance.

- Management of BK virus infection

Key statement

It is recommended that aggressive intervention is recommended when the viral load reaches clinical threshold during regular monitoring of blood/urine BK viral load in kidney transplant recipients. Once the renal function deteriorates, active interventions including renal allograft biopsy, reduction or adjustment of immunosuppressive drugs are strongly recommended. Other add-on treatment, including leflunomide, IVIG, quinolone, maybe helpful. Continuously monitor BK viral load is necessary.

Voting results

Q3-1: In kidney transplant recipients with stable renal function, the BK viral load did NOT reach clinical significance, what will you do in your clinical practices? (multiple choice question)

All experts suggest to closely monitor plasma/urine BK viral load when it did not reach clinical significance in kidney transplant recipients with stable renal function (Table 4).

Q3-2: In kidney transplant recipients with stable renal function, the BK viral load reaches clinical significance, what will you do in your clinical practices? (multiple choice question)

Most experts suggested close monitoring of plasma BK viral load (94%) and reduction of immunosuppressive drugs (94%) when the viral load reached clinical significance in patients with stable renal function. One-third experts will consider renal allograft biopsy to prove BKVAN (Table 4).

Q3-3: In kidney transplant recipients with deteriorated renal function, the BK viral load rises above the threshold of viruria or viremia, what will you do in your clinical practices? (multiple choice question)

When BK viral load reached above the threshold level of viruria or viremia in kidney transplant recipients with deteriorated renal function, all experts suggest to perform renal allograft biopsy, 94% of experts suggest the reduction of immunosuppressive drugs, 82% suggest to closely monitor plasma BK viral load, and 76% suggest to add-on other treatment such as leflunomide, IVIG or quinolone. A total of 12 experts considered to choose all these four options (Table 4).

Comments

Since the definition of clinically significant BK viral load varies among hospital protocols and guidelines (Appendix 3), whether the BK viral load is clinically significant or reaches the threshold are based on hospital criteria or physicians' experience. It is important to note that the viral load measured varies from laboratory to laboratory. The results can be very different, depending on which region of the BK virus gene the primers are designed from. Therefore, each hospital should establish its own dataset first. Another point to note is that even if the viral load tested does not reach clinical significance, a renal biopsy should be performed if suspected. It was reported that no BK viremia or viruria was detected in kidney transplant recipients with biopsy-proven BKVAN.[22,23] Undetected BK viral load may be related to gene mutations and primers used for testing.

Early detection of BK viruria and viremia with histological confirmation is essential for diagnosis and prevention of BKVAN which may develop early even with normal serum creatinine levels. It is quite important for evey transplant institute to set up the indications for renal allograft biopsy in kidney transplant recipients. For patients with risk of BKVAN, such as viremia, performance of kidney biopsy is still recommended even in the absence of elevated serum creatinine.[13]

With the increase of BK viral load and deterioration of kidney function, more and more interventions are being implemented (Figure 3). No effective antiviral therapy has been confirmed to successfully treat BKVAN.[24] Reduction in immunosuppression for BK virus infection in kidney transplant recipients is the primary treatment to date.[2] No randomized controlled trials have provided evidence that adjuvant agents of leflunomide, cidofovir, fluoroquinolones or IVIG, alone or in combination, is superior to immunosuppression reduction alone. A systematic review failed to prove benefit of adding leflunomide or cidofovir to immunosuppression reduction and concluded that adequately powered randomized trials were needed to define the important issue.[25]

- Immunosuppression adjustment

Key statement

The first step of immunosuppression adjustment for the management of BK virus infection is the reduction or discontinuation of mycophenolic acid (MPA) alone or in combination with adding on mammalian target of rapamycin inhibitors or reducing calcineurin inhibitors.

Voting results

Q4-1: In patients with significant BK viral load, what is your FIRST step for immunosuppression adjustment?

Most of the experts (65%) suggest that the first step for the adjustment of immunosuppressive drugs was to reduce or discontinue MPA and add-on mTORi. All experts suggest to reduce or discontinue MPA as the first step for the adjustment of immunosuppressive drugs, and more than half of them (65%) would also add-on mTORi and few of them (12%) would reduce calcineurin inhibitors at the same time (Table 4).

Q4-2: In patients with persist significant BK viral load, what is your FUTHER step for immunosuppression adjustment?

Most of the experts suggest that the further step for immunosuppression adjustment was to further reduce or discontinue MPA and add-on mTORi (29%),or to add-on other treatment (29%) such as leflunomide, IVIG, quinolone or others. 24% of experts suggest to further reduce or discontinue calcineurin inhibitors and add-on mTORi (Table 4).

More than half (53%, 9/17) of experts suggest to further reduce or discontinue MPA or calcineurin inhibitors and add-on mTORi as the further step for immunosuppression adjustment. 41% (7/17) suggest to further reduce or discontinue calcineurin inhibitors alone or in combination with adding on mTORi, or to further reduce calcineurin inhibitors with reduction or discontinuation of MPA (Table 4).

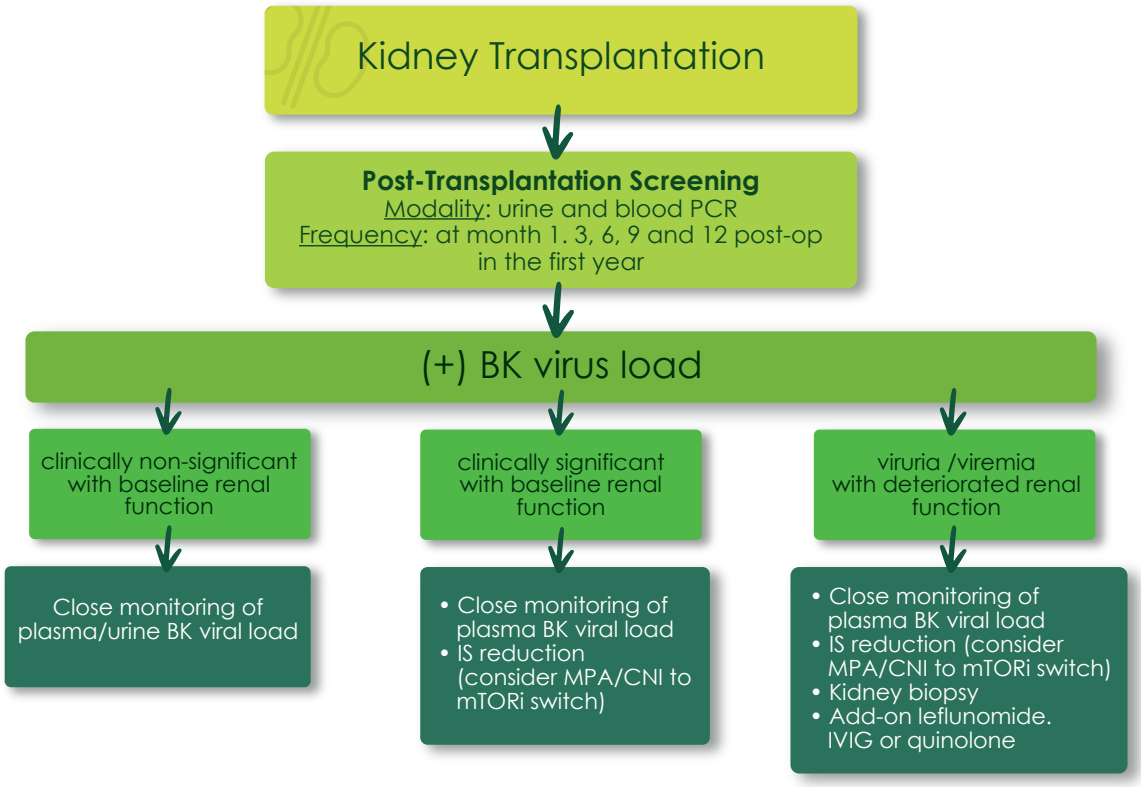
Comments

Management of BKVAN mainly depends on reducing the total immunosuppression.[24] The American Society of Transplantation guideline recommends two strategies: (i) first decrease the calcineurin inhibitors dose by 25-50% in one or two steps, and then the antimetabolite is decreased by 50% and eventually discontinued; (ii) first decrease the antimetabolite by 50%, and then decrease the calcineurin inhibitors by 25–50% and discontinue the antimetabolite.[3] At this time, the "calcineurin inhibitors first" and "antimetabolite first" strategies (as the first step) are considered to be largely equivalent.[7,10,13,26-28]

Another strategy will be to switch from tacrolimus to low-dose cyclosporine, or switch from calcineurin inhibitor to sirolimus, or switch from MPA to low-dose sirolimus, or from MPA to leflunomide.[3] One point to remind is that the calcineurin inhibitors must be reduced when mTORi is on, otherwise there will be a lot of complications. A retrospective study assessed reduction of BK viral load and graft loss in three different protocols: group 1, reduction of calcineurin inhibitors and MPA; group 2, primary switch from calcineurin inhibitors to sirolimus; group 3, secondary switch to sirolimus when reduction in calcineurin inhibitors failed. The results showed that group 3 had the longest total time for BK virus quantitative PCR reduction by 1 log with the highest number of graft losses among the three groups. The authors suggested that in patients who failed general immunosuppression reduction, a switch to mTORi should be performed earlier, at a stage with estimated glomerular filtration rate greater than 25 mL/min.[29]

Immunosuppression is further adjusted based on the blood BK viral load and the course of serum creatinine levels during follow-up tests at least every 2 weeks until BK viremia is cleared or as clinically indicated.[3]

Figure 3. Proposed algorithm for screening and management of kidney transplant recipients with BK virus infection. Abbreviations: PCR, polymerase chain reaction; MPA, mycophenolic acid; CNI, calcineurin inhibitor; mTORi, manmmalian target of rapamycin inhibitor; IVIG, intravenous immunoglobulin.



• CONCLUSION

BK virus infection has a notable impact on renal allograft during the first year after transplantation. Early diagnosis and therapeutic interventions are crucial. This consensus demonstrated the conceptual illustration of screening and management for BK virus infection (Figure 3).

Regular screening for BK virus infection is strongly recommended. Frequent monitoring and renal allograft biopsy are important for any suspicious BK virus infection. Due to the lack of effective antiviral agents, reduction in immunosuppression is the main therapeutic approach. An mTORi-based regimen may be beneficial to treat BKVAN. Clinicians must delicate clinical evaluations to balance allograft rejection and BK virus infection.

Table 4 .Voting results for management

Management of BK virus infection	**Voting results (%, n/N)**
Q3-1. In patients with baseline renal function, the BK viral load did NOT reach clinical significance, what will you do in your clinical practices? (multiple choice question)	
• Immunosuppression reduction	11 (2/18)
• Perform renal allograft biopsy	6 (1/18)
• Closely monitoring of plasma/urine BK viral load	100 (18/18)
Q3-2. In patients with baseline renal function, the BK viral load reaches clinical significance, what will you do in your clinical practices? (multiple choice question)	
• Immunosuppression reduction	94 (17/18)
• Perform renal allograft biopsy	33 (6/18)
• Closely monitoring of plasma BK viral load	94 (17/18)
Q3-3. In patients with deteriorated renal function, the BK viral load reaches viruria or viremia level, what will you do in your clinical practices? (multiple choice question)	
• Immunosuppression reduction	94 (16/17)
• Perform renal allograft biopsy	100 (17/17)
• Closely monitoring of plasma BK viral load	82 (14/17)
• Add-on other treatment (leflunomide or IVIG or quinolone orothers)	76 (13/17)
Immunosuppression adjustment	
Q4-1. In patients with significant BK viral load, what is your FIRST step for immunosuppression adjustment?	
• Reduce or discontinue calcineurin inhibitors	0
• Reduce or discontinue MPA	24 (4/17)
• Reduce or discontinue steroid	0
• Reduce calcineurin inhibitors and reduce or discontinued MPA	12 (2/17)
• Reduce or discontinue calcineurin inhibitors and add-on mTORi	0
• Reduce or discontinue MPA and add-on mTORi	65 (11/17)
Q4-2. In patients with persist significant BK viral load, what is your FUTHER step for immunosuppression adjustment?	
• Further reduce or discontinue calcineurin inhibitors	12 (2/17)
• Further reduce or discontinue MPA	0
• Discontinue steroid	0
• Further reduce calcineurin inhibitors and reduce or discontinued MPA	6 (1/17)
• Further reduce or discontinue calcineurin inhibitors and add-on mTORi	24 (4/17)
• Further reduce or discontinue MPA and add-on mTORi	29 (5/17)
• Add-on other treatment (leflunomide or IVIG or quinolone orothers)	29 (5/17)

Abbreviations : IVIG, intravenous immunoglobulin; MPA, mycophenolic acid; mTORi, mammalian target of rapamycin inhibitor.

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ABBREVIATION LIST

- **BKVAN** : BK Virus-associated nephropathy
- **IVIG** : intravenous immunoglobulin
- **MPA** : mycophenolic acid
- **mTORi** : mammalian target of rapamycin inhibitor
- **PCR** : polymerase chain reaction

APPENDIX

Appendix 1. Post-transplant BK virus Screening Modality and Interval (focus in the first year)

	Screening modality			Timing (month)																						
Month	BP	UP	UC	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
AST-IDCOP[1]	✔			●	●	●	●	●	●	●	●	●			●			●			●			●			●
KDIGO[2]	✔			●	●	●			●			●			●												
UPMC	✔	✔		●	●	●			●			●			●						●						●
MGH[3]	✔			●	●	●	●	●	●		●		●		●		●		●		●		●		●		●
UCLA[4]	✔			●	●	●	●	●	●			●			●												●
UPenn Medicine[5]	✔			●		●			●						●												●
UK[6]	✔	✔		●	●	●	●	●	●		●		●		●			●			●			●			●
Samsung Medical Center, Korea[7†]	✔	✔		●	●	●	●		●			●			●												
Seoul St Mary's Hospital, Korea[8]	✔			●		●			●			●			●												
Australia[9]	✔			●	●	●	●	●	●	●	●	●	●	●	●			●			●			●			●
Sweden[10]	✔					●			●			●			●												
University Hospital Basel, Switzerland[11]	✔		✔	● Every 2 weeks x 3 months			●	●	●						●												●

Abbreviations : BKPyV, BK polyomavirus; BP, blood PCR; UP, urine PCR; UC, urine cytology; PCR, polymerase
chain reaction; AST-IDCOP, American Society of Transplantation Infectious Diseases Community of Practice; KDIGO, The Kidney Disease: Improving Global Outcomes; UPMC, University of Pittsburgh Medical Center; MGH, Massachusetts General Hospital; UCLA, University of California, Los Angeles; UPenn Medicine, University of Pennsylvania Health System; UK, United Kingdom.
*After first year, screening is performed annually up to 5 years post-transplant.
#Screening is performed monthly for the first 3-6 months and then every 3 months until the end of the first year, and screening at least every 3 months for 2 years, then annually for 5 year.
†Urinc PCR was monitorcd at 1, 5, 9, 16, 24, 36, 48, and 52 wecks after kidncy transplantation.

Appendix 2. Current Intervention Strategies for BK virus and BKVAN

Checkpoints	Strategies	Protocol Applied	AST-IDCOP[1]	KDIGO[2]	UPenn, USA[5]	MGH, USA[3]	UCLA, USA[4]	UK[6]	Seoul's St. Mary's Hospital, Korea[8]	Samsung Medical Center, Korea[7]	Australia[9]	University Hospital Basel, Switzerland[11]	Sweden[10]
Determinants of strategy use for IS reduction	Blood/Plasma BK viral load	(5/11)				●	●	●	●				●
	Urine BK viral load	(1/11)								●			
	Level of immunologic risk	(1/11)			●								
	Allograft biopsy	(1/11)									●		
	None	(3/11)	●	●								●	
Strategies for IS reductio (Multiple strategies)	↓ or DC CNI (in any degree)	(4/11)	●	●			●	●			●		
	↓ or DC AM (in any degree)	(4/11)	●	●	●		●	●					
	↓ oral prednisone (in any degree)	(3/11)	●								●		●
	↓ or DC TAC	(4/11)				●					●	●	●
	↓ or DC MMF/MPA	(7/11)		●		●	●	●	●	●	●		●
	Switching TAC → CsA	(3/11)	●	●				●			●		
	Switching CNI → SRL	(1/11)	●										
	Switching MPA → SRL	(1/11)	●										
	Switching MPA → leflunomide	(2/11)	●								●		
	Start mTORi + low dose CsA	(1/11)									●		
Monitoring of clinical response	Blood/plasma BK viremia PCR	(7/11)	●		●	●	●		●			●	●
	Serum creatinine	(3/11)	●		●				●				
Goal of stabilization	↓ in plasma BK viremia more than a certain amount of copies in a certain time period	(3/11)	●		●	●							
	Clearance or negative conversion of plasma BK viral load in a certain time period	(3/11)					●			●		●	
Viremia not resolved after observation period	Further IS reduction step as previous strategies	(2/11)	●										●
	↓ or DC CNI (in any degree)	(3/11)			●		●		●				
	↓ or DC TAC	(2/11)								●		●	
	DC MMF/AM	(1/11)					●						
	Add mTORi	(2/11)								●			
	Transplant/allograft biopsy to r/o acute rejection	(3/11)			●		●		●				
	Consider adjunctive therapies (IVIG or antivirals)	(3/11)				●					●		
After successful clearance of BK viremia	Return to routine maintenance IS	(4/11)	●			●			●			●	
	Monitor DSA, acute rejection, CNI trough level or recurrent viremia	(1/11)			●								
	BK PCR monitoring after IS increase	(1/11)				●							

Abbreviations : BKVAN, BK virus-associated nephropathy; AST-IDCOP, American Society of Transplantation Infectious Diseases Community of Practice; KDIGO, The Kidney Disease: Improving Global Outcomes; UPenn, University of Pennsylvania; MGH, Massachusetts General Hospital; UCLA, University of California, Los Angeles;UK, United Kingdom; IS, immunosuppression; DC, discontinue; CNI, calcineurin inhibitor; AM, antimetabolite; TAC, tacrolimus; MMF, mycophenolate mofetil; MPA, mycophenolic acid; CsA, cyclosporine; SRL, sirolimus; mTORi, manmmalian target of rapamycin inhibitor; PCR, polymerase chain reaction; IVIG, intravenous immunoglobulins; r/o, rule out; DSA, donor-specific antibody.

Appendix 3. Clinically Significant Threshold or Value of BK Viremia/Viruira in guidelines/protocols

Guidelines, Recommendations or Hospital Protocols	Definition of BK Viremia/Viruria
AST-IDCOP[1]	Plasma BK viral load > 1,000 copies/mL (sustained in 2 measurements in < 3 weeks) or plasma BK viral load > 10,000 copies/mL (increased in 1 of 2 measurements in <3 weeks)
KDIGO[2]	Plasma BK viral load >10,000 copies/mL (10^7 copies/L)
UPenn Hospital[5]	Plasma BK viral load >10,000 copies/mL (10^7 copies/L)
UCLA Medical Center[4]	Rising plasma BK virus DNA copies on serial measurements irrespective of BK virus copy levels
MGH[3]	Plasma BK viral load >10,000 copies/mL (10^7 copies/L)
Seoul's St. Mary's Hospital[8]	Plasma BK viral load >10,000 copies/mL (10^7 copies/L)
Samsung Medical Center[7]	Urine BK viral load ≧10,000 copies/ml
UK[6]	Plasma BKPyV load ≥10,000 copies/mL
Australia[9]	Plasma BK viral load ≥1,000 copies/mL
Sweden[10]	Plasma BK viral load >10,000 copies/mL (10^7 copies/L)
University Hospital Basel, Switzerland[11]	Plasma BK viral load ≥1,000 copies/ml in at least two consecutive measurements

Abbreviations : AST-IDCOP, American Society of Transplantation Infectious Diseases Community of Practice; KDIGO, The Kidney Disease: Improving Global Outcomes; UPenn, University of Pennsylvania; UCLA, University of California, Los Angeles; MGH, Massachusetts General Hospital UK, United Kingdom.

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NOTE

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