Management of BK virus in Kidney Transplantation

CLINICAL DECISION SUPPORT TOOL

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European Reference Network
for rare or low prevalence complex diseases
Network Transplantation in Children (ERN TRANSPLANT-CHILD)

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1. Introduction

Kidney transplantation (KT) is often the best renal replacement therapy (RRT) for children with end-stage kidney failure. Compared with dialysis, KT yields a better kidney function, health-related quality of life and patient survival.

Infections remain one of the most common complication in KT. Most infections in the first month after transplant are typically health care-associated, whereas later infections often are community-acquired. Opportunistic infections such as cytomegalovirus (CMV) infection, Epstain-Barr virus (EBV) infection and BK virus (BKV) infection most frequently occur in the first 12 months after transplantation and in parallel with high levels of immunosuppression (1).

In the last 20 years, BKV has evolved from a rare opportunistic infection to a consistently identified complication after KT (2-10). The emergence of BKV-associated nephropathy (BKVAN) as a significant cause of renal allograft loss has occurred in parallel to the introduction of more potent and effective immunosuppressive agents such as tacrolimus and mycophenolate mofetil (MMF), suggesting that a higher level of immunosuppression is an important risk factor for the development of BKVAN. Since BKV viraemia precedes the development of BKVAN, the development of sensitive quantitative polymerase-chain-reaction (qPCR) assays has enabled and facilitated early detection of viremia and allowed pre-emptive strategies to avoid BKVAN.

Primary BKV infection normally is an asymptomatic infection occurring during childhood, with an IgG seroprevalence of >90% in children 5-9 years old (2-10). Approximately 80% of the general population has IgG antibodies against BKV. Later in life there is an age-dependent decline in seroprevalence with 68% of individuals 60–69 years old being IgG positive. It is believed that BKV first replicate in the respiratory tract and that peripheral blood mononuclear cells spread BKV to the urinary tract where the virus establishes a non-replicative latent state in renal tubular epithelial cells and urothelium. In immunocompetent hosts, the virus remains clinically latent, but periodic BKV reactivation may occur, with asymptomatic viruria seen in 7% of healthy adults. The mechanisms behind latency and reactivation of BKV remain poorly understood but cellular immunity probably is vital for viral control (11).

In KT recipients, immunosuppression may disrupt the equilibrium between viral replication and immune response. As a result, uncontrolled replication of BKV can lead to BKVAN and subsequent graft dysfunction and graft loss (2-10). Histologically, BKVAN manifests as a tubulointerstitial nephritis which can mimic acute T cell-mediated rejection (TCMR). Differences include BKV having a predilection for the medulla, intranuclear inclusion bodies,

and positive SV40 viral antigen staining on immunohistochemistry. The virological and immunological factors affecting the progression from self-limited BKV viremia/viruria to BKVAN in KT recipients are not fully known. As for the source of BKV, donor origin has been suggested as the principal source, although reactivation of latent virus in recipients also can occur.

In KT recipients, viruria can be detected in 20-60% of patients, and viremia is seen in 10-20% of patients (2-12). BKVAN occurs in 1-10% of renal allograft recipients, it appears mainly within the first 2 years post-transplantation and causes graft loss in about half of those patients. In most cases, viremia occurs between 3 and 6 months after transplantation, the highest incidence of BKVAN is observed between 5-13 months postoperatively. However, BK-viremia and BKVAN can also occur late after transplantation and should always be considered upon renal dysfunction (2-10).

Anti-viral agents have demonstrated no, or only marginal, effect against BKV, and current treatment strategies mainly involves reducing immunosuppression to improve the capability of the recipient's own immune system to control BKV replication and prevent progression to BKVAN (2-10). At present, no vaccines against BKV are available.

In the paediatric KT population, reported rates of BK viraemia range from 18–37% and BKVAN has been diagnosed in 0–16% of KT patients (2-10), which is slightly more frequently than in adult recipients. Reported rates for graft loss have been variable. In a small case series of patients <20 years of age with BKVAN, 9% of allografts were lost (2) and in the North American Paediatric Renal Trials and Collaborative Studies cohort (NAPRTCS) (4), graft loss occurred in 24% of BKVAN cases and at a mean of 24 months after diagnosis.

Since most primary BKV-infections occurs during childhood, the proportion of patients that lack specific cellular and humoral immunity against BKV is larger in the paediatric KT population. Consequently, BKV might pose a greater risk to paediatric KT recipients compared to adult patients.

According to a large multicentre study by the Cooperative European Paediatric Renal Transplantation Initiative Registry (CERTAIN), the prevalence of BKV-DNAemia in paediatric KT is highest (33.4%) in the first year after transplantation (3). Unlike in adults, a significant proportion of high-level BKV-DNAemia (12.5%) and biopsy-proven BKVAN (21.4%) in paediatric KT recipients occurred >24 months post-transplant and therefore would be missed by many screening protocols recommended for adult KT recipients. In the North American Paediatric Renal Trials and Collaborative Studies cohort (NAPRTCS) (4) graft loss occurred in 24% of BKVAN cases and at a mean of 24 months after diagnosis.

Immunosuppressive protocols in paediatric KT have changed over the last decade (14). Most KT programmes today use maintenance immunosuppression with tacrolimus and MMF and

sometimes with antibody induction therapy (ex. basiliximab, ALG). Some programmes also include corticosteroids but frequently with early withdrawal. As a result of this more potent immunosuppression, acute rejection rates have been reduced. However, this approach has also resulted in higher rates of viral complications, especially in children with primary viral infections.

In rare cases, BKV may cause other manifestations in solid organ transplantation (SOT) patients, such as haemorrhagic cystitis, ureteral stenosis, pneumonia, encephalitis and retinitis. BKVAN is uncommon in other SOT patients and after stem cell transplantation, but it has been described.

Recently, it has been reported that the JC virus (another polyoma virus) also can cause KT dysfunction and mimic BKVAN with positive SV40 IHC staining (13).

2. ADAPTATION PERFORMED BY ERN TRANSPLANTCHILD

Adaptation performed according to the ERN **Handbook #3: Adaptation and Adoption of Clinical Practice Guidelines and Clinical Decision Support Tools for Rare or Low prevalence and Complex Diseases**.

2.1 Name of the document

Consensus guidelines developed by an international working group (IWG), *The Second International Consensus Guidelines on the Management of BK Polyomavirus in Kidney Transplantation. Kotton C et al, on behalf of The Transplantation Society International BK Polyomavirus Consensus Group. Transplantation 2024;108: 1834–1866.*

The target population of this consensus document is KT patients in general, including the paediatric KT population. In the original consensus document, a separate part with specific paediatric consideration is included. In the adaption, any specific recommendations by the International Working Group (IWG) for paediatric KT patients are highlighted.

In the original consensus document developed by the IWG, the quality of evidence is graded according to GRADE as outlined in Table 1 (below), that has shown utility in other clinical guidelines in SOT such as for cytomegalovirus infection (1). Evidence graded A (high level of evidence) were included as recommendations, and evidence graded B or C (moderate to low level of evidence) as suggestions. In the lack of sufficient data and/or evidence, the IWG has included some statements and expert opinions.

Table 1. Quality of evidence, preponderance, and balance considerations for developing recommendations according to Grading of Recommendations, Assessment, Development, and Evaluations (GRADE)

EVIDENCE	PREPONDERANCE	BALANCE
A - HIGH - Well-designed, randomized, controlled studies or diagnostic studies on relevant populations	**STRONG RECOMMENDATION** (we recommend)	
B - MODERATE - Randomized, controlled studies or diagnostic studies with minor limitations; overwhelmingly consistent evidence from observational studies	RECOMMENDATION (we suggest)	
C - LOW -Observational studies (case-control or cohort design)	**RECOMMENDATION** (we suggest)	
D - VERY LOW - Expert opinion, case reports, reasoning from first principles		**NO RECOMMENDATION** (statement)
X - EXCEPTIONAL - Exceptional studies where validating studies cannot be done, and there is a clear preponderance of benefit or harm	**STRONG RECOMMENDATION** (we recommend) **RECOMMENDATION** (we suggest)	**NO RECOMMENDATION** (statement)

(Table adapted from Kotton and al, Transplantation, September 2024, volume 108, number 9, with modifications)

2.2 PICO question

Not used in adaptations of previously published guidelines.

3. Recommendations by the IWG

3.1 Diagnostic Recommendations

I. The IWG recommend regular screening of kidney transplant recipients for BKV replication to identify patients for treatment of probable/presumptive biopsy-proven BKVAN (strong, A).

II. The IWG recommend screening KT recipients for plasma BKV loads monthly until month 9, then every 3rd month until 2 years post transplantation (strong, B).

- **For paediatric KT patients,** the IWG recommend monthly screening for plasma BKV-DNAemia until month 9, then every 3rd month until month 24 posttransplant (strong, B), and suggest further screening every 3rd month until month 36 posttransplant (weak, C).

III. If plasma BKV-DNA loads are 1000–10 000 copies/mL (or equivalent), the IWG suggest confirmatory testing within 2–3 weeks (weak, B).

IV. In KT recipients with sustained plasma BKV-DNA loads >1000 copies/mL (or equivalent), the IWG suggest monitoring BKV-DNAemia every 2–4 week to assess dynamics and response to the intervention (weak, D).

V. In KT recipients requiring increased immunosuppression or antirejection therapy, the IWG suggest resuming monthly screening for BKV-DNAemia for the next 3 months (weak, D).

VI. In resource-limited settings, the IWG recommend using urine cytology for decoy cells as the minimal screening approach (strong, B) at similar time points to the above (weak, D).

VII. If blood sampling is not available or considered inappropriate for screening, the IWG suggest measuring urine BKV-DNA loads by quantitative nucleic acid testing (QNAT) at similar time points as recommended above (weak, D).

VIII. If urine decoy cells or urine BKV-DNA loads of >10 million copies/mL (or equivalent) are detected, the IWG recommend measuring plasma BKV-DNA loads to guide clinical management (strong, B).

IX. For combined kidney/SOT, including pancreas, the IWG suggest extending screening for BKV-DNAemia every 3rd month up to 36 months posttransplant (weak, C).

X. For non-kidney SOT recipients, the IWG recommend to not routinely screen for BKV-DNAemia (strong, B).

XI. For non-kidney SOT recipients presenting with declining renal function, and in the absence of other reasons for the renal compromise, the IWG suggest testing for BKV-DNAemia and looking for BKVAN if a renal biopsy is performed (weak, C).

Specific paediatric recommendations:

For paediatric KT patients, no data exist for specifying a specific threshold for clinically significant BKV-DNAemia loads, and most reports recommend using those proposed for adults.

3.2 Laboratory testing

I. The IWG recommend that the same specimen type and assay be used in the same diagnostic laboratory to avoid uncertainty because of assay variability when monitoring the dynamics of BKV-DNAemia (strong, B).

II. The IWG recommend using QNAT assays that target conserved BKV genome sequences to permit the detection of all genotypes and variants (strong, C).

III. The IWG recommend using QNAT assays with a short amplicon size of <150 base pairs (bp) to avoid significant under-quantification (strong, C).

IV. The IWG recommend that clinical virology laboratories serving transplantation programmes participate in external quality assurance programmes for quantitative BKV-DNA load testing (strong, C).

According to the IWG, BKV-DNAemia loads have a higher positive predictive value for biopsy-proven BKVAN than high-level urine BKV loads. However, high-level viruria precedes plasma BKV-DNAemia by approximately 6 weeks (range 1-12 weeks). Urine viral loads are associated with higher variability and may by outside the assays linear range, which, together with naturally occurring changes in urine composition, may impair decision-making regarding the impact of immunosuppression reduction.

Specific paediatric recommendations:

For paediatric KT patients, no specific laboratory testing is recommended by the IWG.

3.3 Histopathology

I. The IWG recommend that in the context of detectable BKV-DNAemia, a kidney biopsy be performed if clinically indicated (eg, rise in serum creatinine, proteinuria, hematuria; strong, A).

II. The IWG suggest that in the context of detectable BKV-DNAemia and stable renal function, a kidney biopsy should be considered for patients at high immunological risk or high virologic risk (weak, D).

III. The IWG suggest that kidney transplant biopsies be interpreted in the context of clinical, laboratory, and virologic data and prior biopsy findings (weak, C).

IV. The IWG recommend reporting the semiquantitative polyoma virus tissue load (PyVL) score to enable the classification into the Banff Working Group proposal (strong, C).

V. The IWG recommend the parallel reporting of the classification of the American Society of Transplantation (AST-PyVAN) using the 5 strata of PyVAN-A, -B1, -B2, -B3, and -C to accommodate inflammation and tubulitis (strong, C).

VI. The IWG recommend that antibody-mediated rejection be diagnosed in a patient with detectable BKV-DNAemia if Banff diagnostic criteria are met (strong, C).

VII. The IWG recommend that concomitant interstitial TCMR (Banff grade IA/B) is not diagnosed based on inflammation and tubulitis; instead, an explanatory diagnostic comment incorporating interdisciplinary discussion should be used (strong, B).

VIII. The IWG recommend immunohistochemistry (clone PAb 416 against SV40 large T-antigen, LTag) for confirming the diagnosis of BKVAN (strong, A).

IX. The IWG recommend routine SV40 (LTag) immunohistology in patients with detectable BKV-DNAemia (strong, B).

X. The IWG suggest using SV40 (LTag) immunohistology in patients with unknown BKV-DNAemia status with inflammatory changes in the biopsy (weak, D).

XI. The IWG suggest to not use routine SV40 (LTag) immunohistology staining in patients with undetectable BKV-DNAemia (weak, C).

XII. The IWG suggest to NOT perform an allograft biopsy during the course or resolution of BKV-DNAemia/BKVAN unless rejection or another renal disease is a matter of concern, and its detection will alter management (weak, D).

Specific paediatric recommendations:

For paediatric KT recipients with BKV-DNAemia, the IWG recommend performing a kidney biopsy as clinically indicated (eg, rise in serum creatinine, new-onset proteinuria, hematuria) (strong, A)

For paediatric KT patients with stable kidney transplant function and persistent BKV-DNAemia >10 000 copies/mL (or equivalent) despite reducing immunosuppression, the IWG suggest performing a renal allograft biopsy because serum creatinine rise may be delayed in children with significant renal injury including rejection (weak, B).

3.4 Risk Assessment

Risk factors for BKV-DNAemia and biopsy-proven BKVAN are the same for both adult and paediatric KT recipients and listed by the IWG in Table 2 (below).

According to the IWG, donor factors associated with an increased risk of recipient BKV-DNAemia or BKVAN include:

i. Donor urinary BKV shedding
ii. BKV seropositivity with very high donor levels of antibody against BKV major capsid protein (VP1)
iii. Certain donor BKV genotypes and sub-genotypes
iv. BKV genotypes different from the recipient (mismatching)

According to the IWG, recipient factors associated with an increased risk of recipient BKV-DNAemia or BKVAN include:

i. Older recipient age
ii. Male recipient

iii. BKV (VP1) seronegativity (if the donor is seropositive)
iv. Re-transplantation
v. Absence of potentially protective HLA-types (such as A2, A24, B7, B8, B13, B44, B51, Cw7 and DR15) or their combination
vi. Low levels of neutralizing antibodies against donor BKV serotype

According to the IWG, transplantation factors associated with an increased risk of recipient BKV-DNAemia or BKVAN include:

i. Immunosuppression with tacrolimus (compared with cyclosporine A)
ii. Immunosuppression with T-cell depleting agents (such as ALG)
iii. Acute rejection episodes (rejection treatments)
iv. Higher corticosteroid exposure
v. Ureteric stent
vi. AB0-incompatible transplantation (and especially in recipients with high anti-donor A/B IgG titers >1:256)

Registry studies show that immunosuppression using mTOR-inhibitors seem to reduce the risk of BKV-DNAemia and BKVAN (12).

Specific paediatric risk factors:

According to the IWG, specific risk factors for BKV-DNAemia among paediatric KT patients are:

i. Young paediatric recipient age (evidence level: very low, D)
ii. Obstructive uropathy as primary kidney disease (evidence level: very low, D)

The IWG has graded the risk factors according to the quality of the evidence but without making recommendations as to their relevance for interventions. Some of the tests are widely available, many are available in research projects only.

Table 2. Risk factors of BKV-DNAemia and biopsy-proven BKV-nephropathy in kidney transplantation

	BKV-DNAemia[A]		Biopsy-proven BKV-nephropathy[B]	
	RISK FACTOR	**Evidence level[C]**	**RISK FACTOR**	**Evidence level[C]**
DONOR FACTORS	Urinary BKV shedding	**Low, C**	Urinary BKV shedding	**Low, C**
	BKV genotypes and subgenotypes	**Very low, D**	BKV genotypes and subgenotypes	**Very low, D**
	BKV-seropositive antibody[D] status (D^+) if antibody levels are very high in living donors	**Low, C**	BKV genotypes different from the recipient (mismatching)	**Very low, D**
	BKV genotypes different from the recipient (mismatching)	**Very low, D**	LVGR polymorphisms	**Very low, D**
RECIPIENT FACTORS	Older recipient age	**Moderate, B**	Older recipient age	**Low, C**
	Male recipient sex	**Moderate, B**	Male recipient sex	**Low, C**
	BKV-seronegative recipient antibody status (R^-) if the donor is BKPyV-seropositive D^+	**Moderate, B**		
	Low recipient neutralizing antibody[E] levels against the donor BKV serotype	**Very low, D**	Low recipient neutralizing antibody levels[E] against the donor BKV serotype	**Very low, D**
	Previous kidney transplantation	**Low, C**		
	HL A class I (absence of A2, B7, B8, B51, B44, B51, B13, CW7)	**Very low, D**		
	HLA class II (DR15)	**Very low, D**	HLA-E*01:03 vs protective HLA-E*01:01	**Very low, D**
	Interferon-γ gene rs2435061	**Very low, D**		
	Younger pediatric recipient age	**Very low, D**		
	Obstructive uropathy as primary renal disease of pediatric recipients	**Very low, D**		
TRANSPLANTATION FACTORS	Tacrolimus (compared with cyclosporine A)	**High, A**	Tacrolimus (compared with cyclosporine A)	**High, A**
	Lymphocyte-depleting agents	**Low, C**	Lymphocyte-depleting agents	**Low, C**
	Acute rejection	**Low, C**	Acute rejection	**Low, C**
	Corticosteroids (higher maintenance; cumulative, rejection therapy)	**Moderate, B**	Corticosteroids (higher maintenance; cumulative, rejection therapy)	**Moderate, B**
	mTOR inhibitors (decrease risk)	**Low, C**	mTOR inhibitors (decrease risk)	**Low, C**
	Ureteric stents	**Low, C**	Ureteric stents	**Low, C**
	ABOi kidney transplantation	**Low, C**	BKV genome rearranged *NCCR*	**Low, C**

LVGR encodes agnoprotein and capsid proteins Vp1, Vp2, and Vp3. *NCCR* harbors the origin of viral DNA replication and transcription promoter/enhancer elements.

[A] Defined as >1000 c/mL (or equivalent) for >2wk (probable BKV-nephropathy) or increasing >10 000 c/mL or equivalent (presumptive BKV-nephropathy);

[B] Defined as biopsy-proven BKV-nephropathy using histological evidence and demonstrating KV-specific involvement.

[C] Based on a literature review using the GRADE classification;

[D] Measured using ELISA with coated antigens of the major capsid protein Vp1 or the Vp1-derived virus-like particles;

[E] Measured using infectious BKV or pseudovirion preparations;

ABOi, ABO-incompatible; BKV, BK polyomavirus; GRADE, Grading of Recommendations, Assessment, Development, and Evaluations; LVGR, late viral gene region; mTOR, mammalian target of rapamycin; NCCR, noncoding control region.

(Table adapted from Kotton and al, Transplantation, September 2024, volume 108, number 9, with modifications)

3.5 Treatment Recommendations

I. The IWG recommend reducing maintenance immunosuppression (see section 1:3:6 below for detailed guidance) as the primary treatment of sustained BKV-DNAemia/BKVAN in KT patients without high immunologic risk or concurrent acute rejection (strong, B).

II. The IWG suggest reducing immunosuppression when BKV-DNAemia is between 1000–10 000 copies/mL (or equivalent) on 2 measurements within 2–3 weeks (weak, B).

III. The IWG recommend reducing immunosuppression based on 1 measurement BKV-DNAemia >10 000 copies/mL (or equivalent) or if biopsy-proven BKVAN (strong, B).

IV. The IWG recommend reducing immunosuppression for biopsy-proven BKVAN even if plasma BKV-DNA load results needed to confirm the diagnosis are still pending (strong, B).

V. The IWG suggest each transplant centre to develop an institutional algorithm and standard operating procedure of how to reduce immunosuppression in patients with BKV-DNAemia (weak, D).

VI. According to the IWG, there is insufficient data to evaluate the efficacy of switching to mTOR inhibitors for treating BKV-DNAemia or biopsy-proven BKVAN.

VII. The IWG suggest to judiciously re-increase maintenance immunosuppression based on the individual immunologic risk after confirmed BKV-DNAemia clearance, with appropriate screening for BKV-DNAemia (weak, D).

VIII. The IWG suggest testing patients with persistent BKV-DNAemia despite the lowest acceptable immunosuppression for *de novo* DSA if there is evidence of renal dysfunction to assist decisions regarding kidney transplant biopsy (weak, D).

IX. For multiorgan transplant recipients, including KT or non-kidney SOT recipients with BKV-DNAemia or biopsy-proven BKVAN, the IWG suggest a careful reduction of immunosuppression as per above, with close clinical and laboratory monitoring, weighing the risks and benefits of rejection and graft loss (weak, D).

<u>Acute rejection and BKV-DNAemia/BKVAN:</u>

In the absence of data defining the best treatment of acute rejection in patients with ongoing BKV-DNAemia/BKVAN, the IWG state that most experts apply high-dose steroid therapy followed by resuming close monitoring of renal allograft function and at least monthly monitoring of BKV-DNAemia for the next 3 to 6 months (expert opinion).

Specific paediatric recommendations:

According to the IWG, there is no evidence supporting any specific treatment for BKV-DNAemia or biopsy-proven BKVAN in paediatric KT recipients other than reduction of immunosuppression.

3.6 Reducing immunosuppression

General approach:

i. The IWG suggest first confirming that all immunosuppressive drug doses and concentrations are within the institutional target range (weak, C).
ii. The IWG recommend that BKV-DNAemia should be monitored every 2–4 weeks until clearance (strong, B) or stabilizing at plasma viral loads <1000 copies/mL (or equivalent) (weak, C).
iii. For rare patients on the lowest acceptable immunosuppression with detectable BKV-DNAemia <1000 copies/mL, the IWG suggest follow-up of BKV-DNAemia and serum creatinine concentration every 3rd month (weak, D).

Two different strategies to reduce immunosuppression are proposed by the IWG.

Strategy 1: Antimetabolite is reduced first

I. Reduction of the dose of antimetabolite by at least 50%.

i. The IWG suggest further immunosuppression reduction if BKV-DNAemia does not decrease by 10-fold at 4 weeks or does not clear below lower limit of detection (weak, C), as follows:

II. Discontinuation of the antimetabolite and tapering of corticosteroid dose to 5–10 mg/d of prednisone or equivalent, if applicable.

i. The IWG suggest adding prednisone (or equivalent) 5–10 mg/d for patients who are not on corticosteroids to avoid CNI monotherapy (weak, C).

III. If further decrease in immunosuppression is necessary, the IWG suggest a stepwise reduction of the CNI dose (tacrolimus trough target 5 ng/mL; cyclosporine trough target 100 ng/mL; weak, C).

i. The target concentrations for further reduction are not well defined and need to be individualized. Expert opinion and case reports discuss tacrolimus target trough concentrations of 3 ng/mL and cyclosporine target trough concentrations 75 ng/mL followed by tacrolimus target trough of 1.5 ng/mL; cyclosporine target trough of 50 ng/mL (no recommendation — statement only).

<u>Strategy 2: CNI is reduced first.</u>

I. Reduction of the dose of CNI by 25%–50% in 1 or 2 steps to target trough concentrations of tacrolimus of 3–5 ng/mL and cyclosporine trough concentrations of 75–125 ng/mL).

i. The IWG suggest further immunosuppression reduction if BKV-DNAemia does not decrease by 10-fold at 4 weeks or does not clear below the lower limit of detection (weak, C), as follows:

II. Reduction of the antimetabolite by 50% and tapering of corticosteroid dose to 5–10 mg/d of prednisone or equivalent, if applicable.

III. Discontinuation of the antimetabolite.

i. The IWG suggest adding prednisone (or equivalent) 5–10 mg/d for patients who are not on corticosteroids to avoid CNI monotherapy (weak, C).
ii. The target concentrations of further reduction are not well defined and need to be individualized. Expert opinion and case reports discuss tacrolimus target trough concentrations of 3 ng/mL and cyclosporine target trough concentrations of 75 ng/mL followed by tacrolimus target trough of 1.5 ng/ mL; cyclosporine target trough of 50 ng/mL (no recommendation — statement only).

<u>For patients on mTOR-inhibitors:</u>

For KT recipients developing BKV-DNAemia or biopsy-proven BKVAN while receiving a combination of mTOR inhibitors and CNI, the IWG conclude there is insufficient data to guide the reduction of immunosuppression.

According to the IWG, possible approaches include:

i. To first reduce the dose of CNI followed by a reduction of the dose of mTOR inhibitor if needed (expert opinion)
ii. To first switch to low-dose CsA followed by a reduction of the dose of mTOR inhibitor if needed (expert opinion)

For patients on belatacept regimens

For KT recipients developing BKV-DNAemia or biopsy-proven BKVAN while receiving a belatacept-based regimen, the IWG conclude there is insufficient data to guide the reduction of immunosuppression.

According to the IWG, possible approaches include:

i. To first reduce or discontinue the antimetabolite (expert opinion)
ii. To increase the interval of belatacept administration to every 6–8 weeks (expert opinion)
iii. To switch to a low-level CNI-based or mTOR inhibitor–based immunosuppressive regimen (expert opinion)

The IWG also suggest testing KT patients with persistent BKV-DNAemia despite the lowest acceptable maintenance immunosuppression for de novo DSA if there is evidence of renal dysfunction to assist decisions regarding kidney transplant biopsy (weak, D).

Specific paediatric recommendations:

For paediatric KT patients, no specific reduction strategy is recommended by the IWG.

3.7 Adjunctive therapies

Possible adjunctive therapies for BKV-DNAemia and BKVAN.

I. The IWG suggest consideration of intravenous immunoglobulin (IVIG) administration as adjuvant therapy in KT recipients with insufficient response to reduced immunosuppression to facilitate viral clearance (weak, D).
II. The IWG suggest consideration of IVIG administration as adjuvant therapy to prevent acute rejection in recipients with high immunological risk when immunosuppression reduction is necessary to facilitate viral clearance (weak, D).

III. The IWG recommend to NOT use cidofovir to treat BKV-DNAemia/BKVAN in KT recipients (strong, B).
IV. The IWG recommend to NOT use leflunomide to treat BKV-DNAemia/BKVAN (strong, B).
V. The IWG recommend to NOT use fluoroquinolones to prevent or treat BKV-DNAemia or BKVAN in KT recipients (strong, A).
VI. The IWG recommend to NOT use statins to prevent or treat BKV-DNAemia or BKVAN in KT recipients (strong, A).

Specific paediatric recommendations:

For paediatric KT patients, no specific adjunctive therapy is recommended by the IWG.

3.8 Re-transplantation

i. The IWG recommend re-transplantation in otherwise eligible patients who lost their prior allograft from BKVAN (strong, B).
ii. The IWG suggest that BKV-DNAemia be resolved before re-transplantation (weak, C).
iii. The IWG suggest NOT routinely performing graft nephrectomy before re-transplantation in those patients with allograft failure after BKVAN having undetectable BKV-DNAemia (weak, C).
iv. According to the IWG, there is insufficient information to make recommendations on the choice of immunosuppression for a subsequent kidney transplant after a prior kidney transplant failed because of BKVAN.

Specific paediatric recommendations:

For paediatric KT patients, no specific considerations for re-transplantation are recommended.

3.9 Cost-Benefit Analysis

According to the IWG, estimates of the cost-benefit of screening for BKV-DNAemia after KT is difficult to determine due to large variations in implementation. Furthermore, clinical routines vary between KT programmes in many aspects including donor and recipient populations, immunosuppressive protocols, diagnostic testing as well as the clinical approaches to positive screening. In addition, data to support recommendations are limited, only 3 cost-utility models have been evaluated.

However, and despite these limitations, the key findings of the 3 cost-utility models are remarkably consistent. Screening results in net survival benefits and is cost-effective for KT recipients. It is important to note that these studies did not consider screening in other SOTs.

3.10 Considerations in paediatric KT patients

Specific paediatric recommendations in summary:

I. The IWG recommend monthly screening for plasma BKV-DNAemia until month 9, then every 3rd month until month 24 posttransplant (strong, B), and further screening every 3rd month until month 36 posttransplant (weak, C).
II. The IWG recommend reducing maintenance immunosuppression as the primary intervention of sustained BKV-DNAemia, and presumptive, or biopsy-proven BKVAN in paediatric KT patients without concurrent acute rejection (strong, B).

III. For paediatric patients with BKV-DNAemia, the IWG recommend performing a kidney biopsy as clinically indicated (eg, rise in serum creatinine, new-onset proteinuria, hematuria; strong, A).
IV. For paediatric patients with stable KT function and persistent BKV-DNAemia >10 000 copies/mL (or equivalent) despite reducing immunosuppression, the IWG suggest performing a renal allograft biopsy because serum creatinine rise may be delayed in children with significant renal injury including rejection (weak, B).
V. In paediatric KT recipients, the IWG suggest to NOT use adjunctive therapies, including leflunomide, cidofovir, or fluoroquinolones, because of the lack of well-designed studies, poorly documented efficacy, and confounders arising from concomitant reduction in immunosuppression (weak, D).

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5. Comments and additional information from ERN TransplantChild

Applicability in peadiatric KT

The target population of the original consensus document is KT patients in general, including the paediatric KT population. In the original consensus document, a separate part with specific paediatric consideration is included. In the adaption, any specific recommendations by the International Working Group (IWG) for paediatric KT patients are highlighted.

As expected, the level of evidence for recommendations in pediatric KT is obviously lower compared to that in adults. Most studies in paediatric KT patients are retrospective, single-center analyses confounded by patients receiving multiple interventions, often in combination with reduced immunosuppression. Presumably, recommendations proposed for adults are applicable also to paediatric KT patients. As in adults, virological screening and monitoring after KT, histopathological evaluation and timely reduction of immunosuppression for BKV-DNAemia or nephropathy after careful consideration of individual risks are the cornerstones of managing BKV in paediatric KT.

Specific risk factors for BKV-DNAemia among paediatric KT patients are:

i. Young paediatric recipient age
ii. Obstructive uropathy as primary kidney disease

In the specific recommendations given for paediatric KT, minor differences exist when compared to adults:

1. For diagnostic recommendations:
   For paediatric KT patients, monthly screening for 24 months post-transplant is recommended and further screening until month 36 post-transplant is suggested. In adults, screening is only recommended for 24 months.

2. For histopathology:
   For paediatric KT recipients with BKV-DNAemia, a kidney biopsy is recommended if clinically indicated (eg, rise in serum creatinine, new-onset proteinuria, hematuria).

For paediatric KT patients with stable kidney transplant function and persistent BKV-DNAemia >10000 copies/mL despite reducing immunosuppression, a renal allograft biopsy is recommended because serum creatinine rise may be delayed in children with significant renal injury, including rejection.

For other recommendations, there are no differences between paediatric and adult KT patients.
Notably:

1. No data exist for specifying a threshold for clinically significant BKV-DNAemia loads in paediatric KT patients, and most reports recommend using those proposed for adults.
2. No specific laboratory testing is recommended for paediatric KT patients.
3. There is no evidence supporting any specific treatment for BKV-DNAemia or biopsy-proven BKVAN in paediatric KT recipients other than reduction of immunosuppression.
4. For paediatric KT patients, no specific strategy is recommended for reduction of immunosuppression
5. No specific adjunctive therapy (including cidofovir, leflunomide, IVIG and ciprofloxacin) for BKV is recommended for KT patients. However, despite only weak evidence, IVIG could be considered in KT patients with insufficient response to reduced immunosuppression to facilitate viral clearance.
6. No specific considerations for re-transplantation are recommended for paediatric KT patients.

Reducing immunosuppression by withdrawal of corticosteroids

In paediatric KT patients with BKV-DNAemia and/or BKVAN, withdrawal of corticosteroids could be considered in reducing immunosuppression.

Potential risks of reducing immunosuppression

When reducing immunosuppression, the risk of acute or chronic rejection should always be considered and especially in patients with high immunological risk (i.e., patients with pre-transplant DSA, history of acute rejection etc.). Under-immunosuppression could also result in sensitisation and testing for de novo DSA could be considered in patients with signs of renal allograft dysfunction to assist decisions regarding kidney transplant biopsy. Sensitisation to HLA may also complicate future attempts of re-transplantation.

Importance of BKV serostatus

Since most primary BKV-infections occurs during childhood, the proportion of patients lacking specific cellular and humoral immunity against BKV is larger in the paediatric KT population. Consequently, BKV might pose a greater risk to paediatric KT recipients compared to adult patients. Whether recipient and/or donor serostatus affects the clinical impact of BKV after KT remains unknown. Studies have shown an increased risk of BKV-DNAemia and BKVAN when

the donor is BKV-seropositive or the donor antibody levels are high and the recipient is BKV-seronegative or the antibody levels are low. Thus, serological data could possibly improve risk assessment and post-operative monitoring. Today, BKV-serology is not performed in routine clinical practice.

5.1 Ongoing trials and future aspects

Much additional research, including randomised clinical trials, are needed to improve understanding and management of BKV infections in paediatric KT recipients and to increase the level of evidence in future recommendations.

Possible future developments include:

I. Evaluate the role of pretransplant BKV serology (qualitative and quantitative) in donors and recipients to predict the risk of BKV-DNAemia/BKVAN
II. Evaluate differences between primary and reactivated, latent BKV infections
III. Evaluate the role of monoclonal antibody preparations in targeting and neutralizing BKV (sub-) types for preventing or treating BKV-DNAemia/BKVAN (clinical trial?)
IV. Evaluate the role of adoptive T-cell therapy for preventing or treating BKV-DNAemia/BKVAN (clinical trial?)
V. Evaluate the possibility to develop vaccines against BKV
VI. Evaluate the risk of BKV viremia and BKVAN in KT from DCD donors
VII. Develop international standards for qBKV PCR -DNA loads (plasma, whole blood, urine, and tissue) based on defined molecular sequences and copy numbers of early and late viral gene regions
VIII. Define optimal screening and monitoring protocols using, minimizing diagnostic efforts and resources without compromising outcomes
IX. Evaluate the use of donor and recipient BKV serostatus, serotype, and neutralizing antibody pre- and post-transplant
X. Evaluate the role of different BKV serotype/genotypes in increasing the rate, severity, and duration of BKV-DNAemia/BKVAN and to guide reducing immunosuppression
XI. Develop and evaluate BKV-specific T-cell mediated immunity assays and thresholds pre- and post-transplant to predict and protect from BKV-DNAemia/BKVAN
XII. Develop and evaluate new treatments for BKV, including viral replication inhibitors

Ongoing clinical trials on BKV

According to clinicaltrials.gov, 57 studies are currently registered as ongoing (October 2025) which include the subject “BKVAN after Kidney Transplantation”. Some studies evaluate new treatments such as virus-specific cytotoxic T-lymphocytes (VST).

6. Abbreviations

ALG: Anti-lymfocyte globuline

BKV: BK virus

BKVAN: BK virus-associated nephropathy

CCS: Clinical consensus statement

CDST: Clinical Decision Support Tool(s)

CMV: Cytomegalo virus

CNI: Calcineurin inhibitor

CPG: Clinical Practice Guidelines

CsA: Cyclosporine A

DSA: Donor specific antibodies

EBV: Epstein-Barr virus

ERN: European Reference Network

HaDEA: European Health and Digital Executive Agency

IVIG: Intravenous immunoglobulin

IWG: International working group

KRT: Kidney Replacement Therapy

KT: Kidney Transplantation

LTag: Large tumor antigen

mTOR: Mammalian target of rapamycin

PCR: Polymerase chain reaction

PICO: Population Intervention Comparison Outcome

PyVL: Polyoma tissue virus load

QNAT: Quantitative nucleic acid testing

SOT: Solid Organ Transplantation

SV40: Simian virus 40

TCMR: T cell-mediated rejection

WP: Work Package

7. ERN TransplantChild adaptation working group

ERN TransplantChild			
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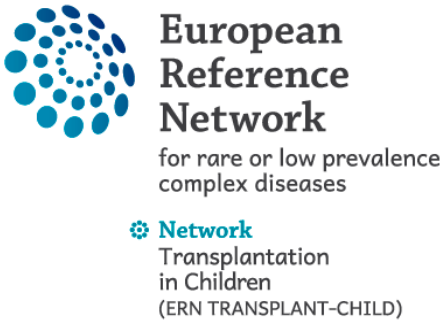

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