Pediatric Nephrology (2025) 40:835–848
https://doi.org/10.1007/s00467-024-06501-7

ORIGINAL ARTICLE

Risk of cellular or antibody-mediated rejection in pediatric kidney transplant recipients with BK polyomavirus replication—an international CERTAIN registry study

Alexander Fichtner[1] · Jeremy Schmidt[1] · Caner Süsal[2,3] · Andrea Carraro[4] · Jun Oh[5] · Matthias Zirngibl[6] · Sabine König[7] · Isabella Guzzo[8] · Lutz T. Weber[9] · Atif Awan[10] · Kai Krupka[1] · Paul Schnitzler[11] · Hans H. Hirsch[12,13] · Burkhard Tönshoff[1] · Britta Höcker[1]

Received: 17 April 2024 / Revised: 9 August 2024 / Accepted: 12 August 2024 / Published online: 11 October 2024
© The Author(s) 2024

Abstract

Background In kidney transplant recipients (KTR), BK polyomavirus-associated nephropathy (BKPyVAN) is a major cause of graft loss. To facilitate the clearance of BKPyV-DNAemia, reduction of immunosuppression is currently the treatment of choice but may increase the risk of graft rejection.

Methods This international CERTAIN study was designed to determine the risk of alloimmune response and graft dysfunction associated with immunosuppression reduction for BKPyV treatment in 195 pediatric KTR.

Results BKPyV-DNAemia was associated with a more than twofold increased risk of late T cell-mediated rejection (TCMR) (HR 2.22, $p=0.024$), of de novo donor-specific HLA antibodies (dnDSA) and/or antibody-mediated rejection (ABMR) (HR 2.64, $p=0.002$), and of graft function deterioration (HR 2.73, $p=0.001$). Additional independent risk factors for dnDSA/ABMR development were a higher HLA mismatch (HR 2.72, $p=0.006$) and re-transplantation (HR 6.40, $p=0.000$). Other independent predictors of graft function deterioration were TCMR (HR 3.98, $p=0.003$), higher donor age (HR 1.03, $p=0.020$), and re-transplantation (HR 3.56, $p=0.013$).

Conclusions These data indicate that reduction of immunosuppression for BKPyV-DNAemia management is associated with increased alloimmune response in pediatric KTR. Therefore, regular dnDSA screening and close monitoring of graft function in case of BKPyV-DNAemia followed by subsequent reduction of immunosuppressive therapy are recommended.

Keywords Pediatric kidney transplantation · Donor-specific antibodies · BK polyomavirus-associated nephropathy · Kidney transplant rejection

Abbreviations

ABMR	Antibody-mediated rejection
AZA	Azathioprine
BKPyV	BK polyomavirus
BKPyVAN	BK polyomavirus-associated nephropathy
CERTAIN	Cooperative European Paediatric Renal Transplant Initiative
CI	Confidence interval
CNI	Calcineurin inhibitor
CSA	Cyclosporine microemulsion
DGF	Delayed graft function
DNA	Deoxyribonucleic acid
dnDSA	*De novo* Donor-specific HLA antibodies
eGFR	Estimated glomerular filtration rate
EVR	Everolimus
HR	Hazard ratio
IVIG	Intravenous immunoglobulin
IL-2R	Interleukin 2 receptor
KTR	Kidney transplant recipient
MFI	Mean fluorescence intensity
MMF	Mycophenolate mofetil
mTORi	Mammalian target of rapamycin inhibitor
NAT	Nucleic acid testing
SIR	Sirolimus
TAC	Tacrolimus
TCMR	T cell-mediated rejection

Extended author information available on the last page of the article

Introduction

In kidney transplant recipients, reactivation of BK polyomavirus (BKPyV) replication is a common consequence of immunosuppressive therapy, which can progress to BKPyV-associated nephropathy (BKPyVAN), and ultimately to graft loss [1]. Additionally, primary BKPyV infection can occur in BKPyV-naïve pediatric kidney transplant patients who lack BKPyV-specific cellular and humoral immunity [2, 3]. The rate of BKPyV-DNAemia is highest (33%) in the first post-transplant year. However, about 10% of pediatric patients do not develop BKPyV-DNAemia until only after the second post-transplant year [4]. High levels of BKPyV-DNAemia are also more common in pediatric patients than in adults. According to the North American Pediatric Renal Trials Collaborative Studies (NAPRTCS), 24% of pediatric kidney allograft recipients with BKPyVAN experience graft loss at an average of 24 months after diagnosis [5].

To date, antiviral agents with BKPyV-specific activity are lacking. Adjunctive therapies, including leflunomide, fluoroquinolones, and IVIG administration, have been evaluated in small studies in adult patients, with variable response rates [5–10]. Therefore, reduction of immunosuppression is currently the only effective strategy to reduce BKPyV-DNAemia and thus to prevent progression to BKPyVAN [1]. However, measures to reduce immunosuppression are not standardized and vary among transplant centers. Reduction or discontinuation of antiproliferative agents or calcineurin inhibitors are the most common approaches, but switching from a calcineurin inhibitor to a mammalian target of rapamycin (mTOR) inhibitor has also been performed to reduce BKPyV-DNAemia [11].

While reduction of immunosuppression is intended to facilitate BKPyV clearance by enhancing the patient's BKPyV-specific cellular and humoral immune response, it may also carry the risk of an increased immune response to the allograft. A number of retrospective, single-center studies in adult kidney transplant recipients have addressed the potential relationship between BKPyV-DNAemia, reduction of immunosuppression, and the development of de novo HLA donor-specific antibodies (dnDSA) and/or transplant rejection, with mixed results [12–25]. Data in the pediatric kidney transplant population are scarce [26, 27].

The objective of this study was to determine the risk of alloimmune responses, namely T cell-mediated rejection (TCMR) and development of dnDSA and/or antibody-mediated rejection (ABMR), resulting from the reduction of immunosuppression for BKPyV-DNAemia management purposes in pediatric kidney allograft recipients. An additional objective was to evaluate risk factors for graft dysfunction in this patient population.

Materials and methods

Study design and patients

We performed a retrospective, international, multicenter, longitudinal cohort analysis of data reported to the Cooperative European Paediatric Renal Transplant Initiative (CERTAIN) registry (www.certain-registry.eu) [28, 29]. This registry allows an in-depth characterization of specific patient cohorts, due to its detailed and comprehensive data collection. Specific and additional data collection for this analysis was performed according to a defined protocol. Eligible patients were pediatric kidney allograft recipients (i) aged ≤ 21 years at the time of transplantation; (ii) with a complete and validated data set; (iii) with plasma BKPyV surveillance by nucleic acid testing (NAT) at least twice during the first year post-transplant and yearly thereafter; (iv) with dnDSA surveillance at least once a year, and (v) with at least 1 year of follow-up post-transplant. All diagnostic investigations for BKPyV or dnDSA events had to be documented including those that were negative. Study centers were asked to enroll all patients who met the above-mentioned inclusion criteria in order to avoid a selection bias. A total of 195 pediatric patients from 8 European pediatric renal transplant centers, who underwent kidney transplantation between 2007 and 2019, were included in the study. Patient and transplant characteristics are shown in Table 1. A subgroup analysis was performed in patients at low immunologic risk ($n = 154$), who were defined as those without re-transplantation, preformed HLA donor-specific antibodies, or desensitization treatment (induction therapy with rituximab or thymoglobulin, plasmapheresis, immunoadsorption). Data were collected on day 0 before transplantation, at months 1, 3, 6, 9, and 12 post-transplant, and every 6 months thereafter. Written informed consent was obtained from all parents/guardians to participate in the registry, with assent from patients when appropriate for their age. The CERTAIN registry was approved by the ethics committee of each contributing center and is fully compliant with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The study was designed, analyzed, and reported according to the STROBE guidelines (https://www.strobe-statement.org).

BKPyV replication and BKPyVAN

Assessment of BKPyV-DNAemia and BKPyVAN was performed according to center practice. Quantitative nucleic acid testing (QNAT) was performed using commercially available assays. Patients with quantifiable BKPyV-DNA detection in the blood (above the lower limit of quantification) were regarded as BKPyV-DNAemia positive.

Table 1 Baseline and transplant characteristics of the entire patient cohort

Parameter	Entire cohort ($n=195$)	BKPyV-DNAemia ($n=59$)	No BKPyV-DNAemia ($n=136$)	P value
Age at KTx, years (median, IQR)	11.2 (5.2–14.7)	8.25 (4.4–13.4)	12.0 (5.79–15.1)	**0.011**
Male gender, *n* (%)	114 (58.5)	39 (66.1)	75 (55.2)	0.205
Caucasian, *n* (%)	184 (94.4)	55 (93.2)	129 (94.9)	0.908
> 1 KTx, *n* (%)[a]	17 (8.7)	3 (5.1)	14 (10.3)	0.364
Living donation, *n* (%)	63 (32.3)	18 (30.5)	45 (33.1)	0.852
Donor age, years (median, IQR)	36.0 (14–45)	28.0 (13.5–43.0)	38.0 (14.0–46.0)	0.314
Cold ischemia time, hours (median, IQR)	10.0 (3.0–14.3)	10.0 (2.9–15.2)	10.0 (3.0–14.1)	0.687
HLA mismatch, *n* (mean ± SD)	2.6 ± 1.2	2.47 ± 1.25	2.61 ± 1.17	0.472
HLA-DR mismatch, *n* (mean ± SD)	0.82 ± 0.61	0.86 ± 0.66	0.79 ± 0.60	0.513
Delayed graft function, *n* (%)	15 (7.7)	3 (5.1)	12 (8.9)	0.544
Preformed HLA donor-specific antibodies (DSA)	23 (11.8)	6 (10.2)	17 (12.5)	0.810
Initial eGFR, mL/min·1.73 m^2 (mean ± SD)[b]	77.0 ± 29.9	77.5 ± 24.3	76.8 ± 32.1	0.462
Initial immunosuppressive regimen[c]				
Plasmapheresis, *n* (%)	8 (4.1)	0	8 (5.9)	0.109
Immunoadsorption, *n* (%)	3 (1.6)	0	3 (2.2)	0.555
Rituximab, *n* (%)	5 (2.6)	1 (1.7)	4 (2.9)	1.000
Thymoglobulin, *n* (%)	10 (5.1)	3 (5.1)	7 (5.2)	1.000
IL-2R antibody induction, *n* (%)	64 (32.8)	17 (28.8)	47 (34.6)	0.536
Maintenance immunosuppression				
TAC, *n* (%)	167 (85.6)	54 (91.5)	113 (83.1)	0.187
CSA, *n* (%)	28 (14.4)	5 (8.5)	23 (16.9)	0.187
MMF, *n* (%)	173 (88.7)	50 (84.8)	123 (90.4)	0.364
EVR, *n* (%)	12 (6.2)	5 (8.5)	7 (5.2)	0.517
AZA, *n* (%)	10 (5.1)	4 (6.8)	6 (4.4)	0.494
Steroids, *n* (%)	193 (99.0)	58 (98.3)	135 (99.3)	1.000
TAC/MMF, *n* (%)	150 (76.9)	47 (79.7)	103 (75.7)	0.680
TAC/EVR, *n* (%)	8 (4.1)	3 (5.1)	5 (3.7)	0.700
TAC/AZA, *n* (%)	9 (4.6)	4 (6.8)	5 (3.7)	0.458
CSA/MMF, *n* (%)	23 (11.8)	3 (5.1)	20 (14.7)	0.095
CSA/EVR, *n* (%)	4 (2.1)	2 (3.4)	2 (1.5)	0.586
CSA/AZA, *n* (%)	1 (0.5)	0	1 (0.7)	1.000
Pediatric Vasudev score (mean ± SD)[d,e]	14.6 ± 5.1	15.3 ± 5.4	14.4 ± 4.9	0.210

BKPyV BK polyomavirus, *KTx* kidney transplantation, *HLA* human leukocyte antigen, *DSA* donor-specific antibodies, *eGFR* estimated glomerular filtration rate, *IL-2R* interleukin 2 receptor, *TAC* tacrolimus, *CSA* cyclosporine microemulsion, *MMF* mycophenolate mofetil, *EVR* everolimus, *AZA* azathioprine

[a]For patients having undergone more than one kidney transplantation, only the most recent one was evaluated

[b]Defined as eGFR at 30 days of post-transplant. eGFR was calculated according to the revised Schwartz formula: eGFR = (mL/min·1.73 m^2) = 0.413 × [height (cm)/serum creatinine (mg/dL)]

[c]Until day 30 of post-transplant

[d]Defined in ref. 4, 31

[e]At 30 days of post-transplant

High-level BKPyV-DNAemia was defined as > 10^4 copies/mL according to international guidelines [1]. Biopsy-proven BKPyVAN was diagnosed by the local pathologist at each center according to the respective most recent Banff classification [30].

Immunosuppressive regimen and treatment of BKPyV replication and BKPyVAN

Immunosuppressive therapy typically included a calcineurin inhibitor (CNI), namely tacrolimus (TAC) or

cyclosporine microemulsion (CSA), an antiproliferative agent, namely mycophenolate mofetil (MMF), azathioprine (AZA) or mammalian target of rapamycin inhibitor (mTORi) such as everolimus (EVR) or sirolimus (SIR), and glucocorticoids (Table 1). The net state of immunosuppression was calculated for each patient using a semi-quantitative immunosuppression score called the modified Vasudev score (Supplemental Table 1) [4, 31]. Treatment of BKPyV-DNAemia and BKPyVAN was performed at the discretion of the treating physician, including reduction of immunosuppressive medication and adjunctive therapy (fluoroquinolones, cidofovir, intravenous immunoglobulins [IVIG]).

Donor-specific HLA antibodies

Patient sera were tested for HLA antibodies and their specificities according to center practice, at least once annually and at the time of an indication biopsy. LABScreen Luminex kits from One Lambda (Canoga Park, CA, USA) were used. Irrespective of the individual definition of DSA-positivity in the participating centers, a mean fluorescence intensity (MFI) of ≥ 1400 was defined as a universal cut-off value indicating DSA positivity in this multicenter setting [32]. Any new antibody was considered de novo whereas an antibody present at the allelic level before and after transplantation was considered preformed.

Graft function and rejection episodes

Graft function was assessed as estimated glomerular filtration rate (eGFR) which was calculated according to the revised Schwartz formula: eGFR = (mL/min per 1.73 m^2) = 0.413 × [height (cm)/serum creatinine (mg/dL)] [33, 34]. Graft function deterioration was defined as an eGFR < 30 mL/min·1.73 m^2 or an eGFR decline ≥ 50% of baseline (at month 1 post-transplant). Biopsy-proven rejection episodes (T cell-mediated rejection (TCMR) and or antibody-mediated rejection (ABMR)) and other histopathologic findings were diagnosed by the local pathologist at each center according to the respective most recent Banff classification (2019) [30]. In this study, all biopsies were indication biopsies. Histopathological signs of TCMR in addition to detection of SV40Ag were not diagnosed as TCMR but BKPyVAN. In the absence of SV40Ag detection, histopathological findings of TCMR were diagnosed as TCMR. Since the issue of TCMR diagnosis under ongoing BKPyV-DNAemia can be difficult and is currently discussed controversially in the literature, we performed two analyses, one including and a second excluding TCMR episodes during BKPyV-DNAemia.

Statistical analyses

Data were analyzed using PASW (SPSS) Statistics 27.0 and R 3.62. Results for continuous variables are given as mean ± standard deviation or median (interquartile range), depending on whether they were normally distributed or not. Categorical parameters are expressed as the number and percentage of patients. The Shapiro–Wilk test was used to assess whether the data were normally distributed. After testing the proportional hazards assumption, Cox regression models with time-dependent variables were used to examine the association of factors with the development of (i) TCMR, (ii) dnDSA and/or ABMR, and (iii) eGFR loss. Covariates included recipient and donor age, sex, ethnicity, cold ischemia time, donor type, re-transplantation, HLA mismatch, delayed graft function (DGF), desensitization treatment, panel reactive antibody level, preformed DSA, level of BKPyV viral load, persistence of BKPyV viral load, clearance of BKPyV and immunosuppressive medication. Factors with a P value < 0.20 according to univariate analysis were included in the multivariable model. Furthermore, an alternative approach was employed for the analysis of data in order to reinforce the results of the time-dependent Cox regression analysis (Kaplan–Meier analysis with a fixed landmark at 12 months post-transplant). Patients who were lost to follow-up or did not reach an observation period of 5 years post-transplant were censored as having no event. The course of the modified Vasudev score during the first year post-transplant was modelled with a mixed linear model and illustrated by segmented linear regression plots. A two-tailed P value < 0.05 was considered statistically significant. All analyses were exploratory, not confirmatory.

Results

Patient cohort

A total of 195 pediatric patients who underwent kidney transplantation between 2007 and 2019, were included in this study. Patient demographics, clinical parameters, and initial immunosuppressive regimen are shown in Table 1. One-year patient and graft survival rates were 100%; at 5 years post-transplant, patient and graft survival rates (uncensored for death) were 98.9% (92/93) and 95.7% (89/93), respectively (Figs. 1 and 2).

BKPyV-DNAemia

One-third of patients (59/195, 30.3%) developed BKPyV-DNAemia during the 5-year study period, with a median onset at 5.6 (IQR, 2.5–10.2) months post-transplant; the majority

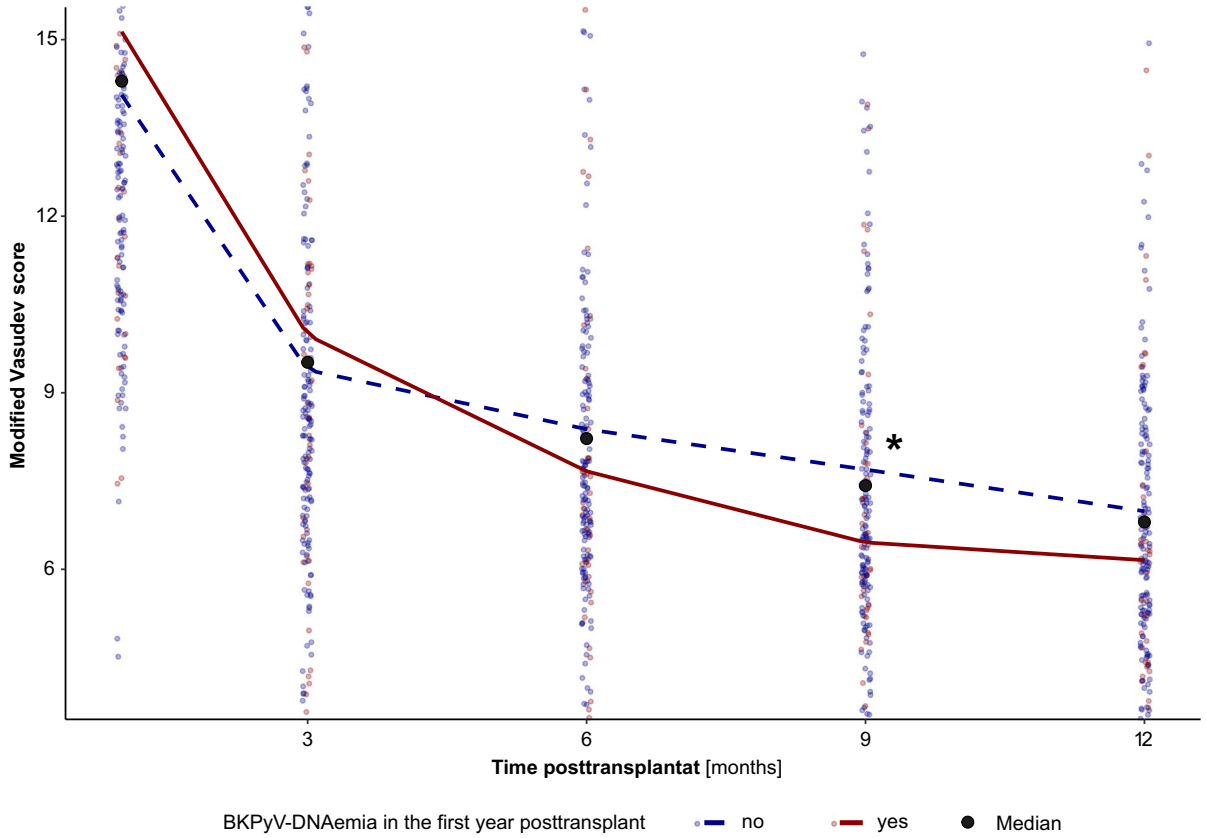


Fig. 1 Segmented linear regression of the modified Vasudev score in patients with and without BKPyV-DNAemia (1-year data). Asterisk (*) marks the point of time with a significant difference in the modified Vasudev score between the two groups (p = 0.022). The slope of the Vasudev score decline between months three and six was also found to be significantly different (p = 0.013). The plot has been magnified in order to enhance the visibility (comparable full scale in Figure S1)

of these patients (45/59, 76.3%) had BKPyV-DNAemia already within the first year post-transplant. The overall rate of BKPyV-DNAemia during the first post-transplant year was 23.1% (45/195). High-level BKPyV-DNAemia (> 10^4 copies/mL) was observed in 35/195 (17.9%) recipients. Thirty-five of 59 patients with BKPyV-DNAemia underwent a transplant kidney biopsy. Biopsy-proven BKPyVAN was diagnosed in 13/195 (6.7%) patients and in (13/59) 22.0% of patients with BKPyV-DNAemia. All patients with biopsy-proven BKPyVAN showed high-level BKPyV-DNAemia. The median time from BKPyV-DNAemia to BKPyVAN was 8.13 months (4.01–11.4). Treatment of BKPyV-DNAemia and BKPyVAN included CNI dose reduction or discontinuation (42/59, 71.2%), MMF dose reduction or withdrawal (20/59, 33.9%), switching from TAC to CSA (9/59, 15.3%), switching from MMF to EVR (7/59, 11.9%), or a combination of these measures. The net state of immunosuppression, as expressed by the modified Vasudev score, is depicted in Fig. 1 and Supplemental Figure S1 (1-year data). As can be seen, the reduction in the total immunosuppressive burden was significantly more pronounced in patients with BKPyV-DNAemia than the standard reduction of immunosuppression after transplantation in patients without BKPyV-DNAemia. Adjunctive therapy included administration of fluoroquinolones (6/59, 10.2%), cidofovir (8/59, 13.4%), and IVIG (7/59, 11.9%). A total of 47 (79.7%) patients cleared BKPyV-DNAemia during the study period. Among those with high-level BKPyV-DNAemia, 26 (74.4%) showed BKPyV-DNAemia clearance including four patients (30.8%) with BKPyVAN. The median time to BKPyV-DNAemia clearance was 4.17 months (2.12–18.6).

T cell-mediated rejection

In the first year post-transplant, 56 (28.7%) patients developed TCMR. Late TCMR (more than 12 months of post-transplant) was observed in 34 patients during the second and fifth year post-transplant. The time from transplantation to TCMR development was significantly ($p = 0.001$) longer in patients with BKPyV-DNAemia (median 18.4 months, IQR 4.69–30.7) than in BKPyV-DNAemia-free (median 3.70, IQR 0.56–11.31) patients. The median time from onset of BKPyV-DNAemia to

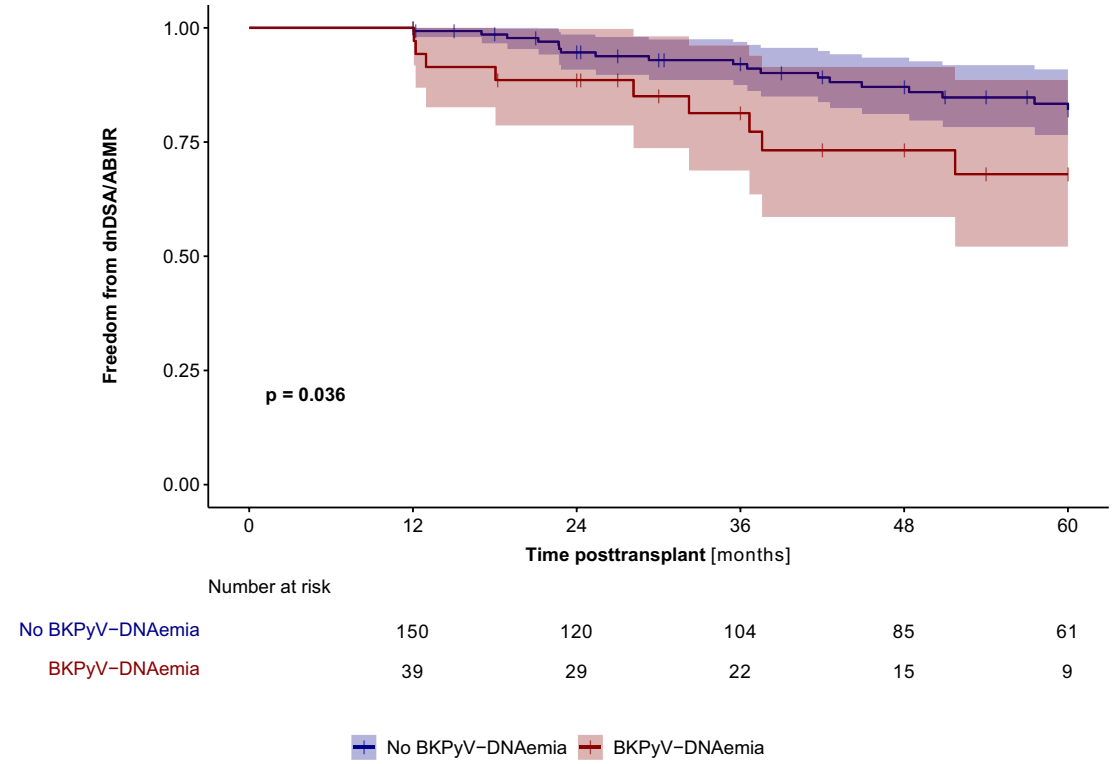


Fig. 2 Freedom from de novo HLA-DSA (dnDSA) positivity and/or antibody-mediated rejection (ABMR) in patients (entire cohort, n = 195) with (red line) and without (blue line) BKPyV-DNAemia during the first 12 months of post-transplant (landmark analysis). BKPyV-DNAemia was significantly associated with the development of dnDSA/ABMR (p = 0.036)

TCMR was 12.3 months (5.71–18.3). According to univariate Cox regression with time-dependent covariate analysis of TCMR development, BKPyV-DNAemia was significantly (HR 2.22, $p = 0.024$) associated with an increased risk of late TCMR (> 12 months post-transplant), presumably due to reduced immunosuppression chosen as treatment for BKPyV-DNAemia. At 9 months post-transplant, the overall immunosuppression score (modified Vasudev score) was indeed significantly lower in patients with BKPyV-DNAemia than in BKPyV-free transplant recipients, namely 6.86 ± 2.99 *vs.* 7.73 ± 3.03 ($p = 0.0479$), whereas the initial immunosuppression score at 30 days post-transplant was comparable between the groups (modified Vasudev score, 15.32 ± 5.41 *vs.* 14.35 ± 4.93, $p = 0.210$). A detailed course of the modified Vasudev score in the first year post-transplant is provided in Fig. 1 and Supplemental Figure S1.

In this study, ten patients were treated for biopsy-confirmed TCMR (being negative for SV40Ag) diagnosed during ongoing BKPyV-DNAemia. If these patients were excluded from the analysis, no significant association of BKPyV-DNAemia and late TCMR was observed. No independent risk factor for the development of TCMR was identified (data not shown).

De novo donor-specific HLA antibodies and antibody-mediated rejection

Forty-nine of 195 patients (25.1%) developed dnDSA during 5 years of follow-up, with a median onset at 12.9 (IQR, 3.6–33.6) months post-transplant. Twenty-two (11.3%) recipients developed dnDSA within the first year post-transplant; 14.4% of patients developed class II dnDSA only, 7.2% had both class I and II dnDSA, and 3.6% had solely class I dnDSA. According to multivariable Cox regression analysis with time-dependent covariates, independent risk factors for the development of dnDSA were BKPyV-DNAemia (HR 2.61, $p = 0.004$), a higher HLA mismatch (HR 3.13, $p = 0.005$), and re-transplantation (HR 4.87, $p = 0.000$) (Table 2). Fifty-six of 195 patients (28.7%) developed dnDSA and/or ABMR during the observation period. The median time from onset of BKPyV-DNAemia to the first detection of dnDSA/ABMR was 15.6 months (8.39–29.4). The rate of dnDNA and/or ABMR was significantly higher in patients with BKPyV-DNAemia (24/59, 40.7%) than in those without (32/136, 23.5%, $p = 0.024$). In addition, patients with BKPyV-DNAemia in the first 12 months of post-transplant developed dnDSA/ABMR significantly

Table 2 Risk factors analysis

	Unadjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Risk factors for developing dnDSA and/or ABMR				
Entire cohort				
BKPyV-DNAemia[#]	2.24 (1.21–4.18)	0.011	2.64 (1.41–4.94)	0.002
Higher HLA mismatch	2.62 (1.32–5.20)	0.005	2.72 (1.34–5.56)	0.006
Re-transplantation	5.75 (2.99–11.1)	0.000	6.40 (3.30–12.4)	0.000
Low immunologic-risk patients				
BKPyV-DNAemia[#]	2.83 (1.35–5.96)	0.006	2.79 (1.33–5.87)	0.007
Higher HLA-DR mismatch	2.01 (1.15– 3.52)	0.015	1.98 (1.14–3.46)	0.016
Risk factors for eGFR loss				
Entire cohort				
BKPyV-DNAemia[#]	2.45 (1.20–5.02)	0.015	2.73 (1.22–6.07)	0.014
TCMR[#]	4.94 (2.02–12.1)	0.000	3.98 (1.61–9.80)	0.003
Higher donor age (years)	1.04 (1.01–1.07)	0.008	1.03 (1.01–1.06)	0.020
Re-transplantation	4.38 (1.76–10.9)	0.001	3.56 (1.30–9.75)	0.013
dnDSA/ABMR[#]	2.37 (1.16–4.87)	0.018		
Low immunologic-risk patients				
BKPyV-DNAemia[#]	4.47 (1.78–11.2)	0.001	4.51 (1.79–11.4)	0.001
TCMR[#]	5.12 (1.71–15.3)	0.004	5.14 (1.72–15.4)	0.004

BKPyV BK polyomavirus, *dnDSA* de novo donor-specific antibodies, *ABMR* antibody-mediated rejection, *HLA* human leukocyte antigen, *eGFR* estimated glomerular filtration rate, *TCMR* T cell-mediated rejection

[#]Variable included as time-dependent variable in the Cox regression model

($p = 0.036$) earlier than BKPyV-DNAemia-free patients (landmark analysis Kaplan–Meier, Fig. 2). According to multivariable Cox regression analysis with time-dependent covariates, independent risk factors for the development of dnDSA and/or ABMR were BKPyV-DNAemia (HR 2.64, $p = 0.002$), a higher HLA mismatch (HR 2.72, $p = 0.006$), and re-transplantation (HR 6.40, $p = 0.000$) (Table 2).

Graft function

Graft function deterioration, defined as an eGFR < 30 mL/min·1.73 m^2 or an eGFR decline ≥ 50% of baseline, occurred in 30 (15.4%) patients during the observation period. The incidence of this event (eGFR < 30 mL/min·1.73 m^2 or an eGFR decline ≥ 50% of baseline) was significantly ($p = 0.019$) higher in pediatric kidney allograft recipients with BKPyV-DNAemia (15/59, 25.4%) than in those without (15/136, 11.0%). The median time from onset of BKPyV-DNAemia to graft function deterioration was 22.0 months (10.1–51.1). According to univariate Cox regression analysis with time-dependent covariates, BKPyV-DNAemia, TCMR, dnDSA/ABMR, older donor age, and re-transplantation were associated with eGFR loss. However, multivariable modeling revealed only BKPyV-DNAemia (HR 2.73, $p = 0.003$), TCMR (HR 3.87, $p = 0.003$), older donor age (HR 1.03, $p = 0.020$), and re-transplantation (HR 3.56, $p = 0.013$) as independent risk factors for eGFR loss in this patient population (Table 2 and Supplemental Table S2).

Subgroup analysis of patients with low immunologic risk

One hundred fifty-four of 195 patients (79.0%) had a low immunologic risk profile. Patient characteristics and clinical parameters are shown in Table 2. Approximately one-third of patients received a kidney from a living donor. Delayed graft function occurred in 5.8% of patients. The majority of patients received an initial immunosuppressive regimen consisting of TAC, MMF, and steroids; and 39.0% received IL-2R antibody induction therapy (Table 3).

One-third of patients (48/154, 31.2%) developed BKPyV-DNAemia over the 5-year study period, with a median onset at 5.5 (IQR 2.6–9.6) months after transplantation. The rate of patients with TCMR (including treated borderline rejection) was 26.0% (40/154) in the first post-transplant year. Late TCMR occurred in 27 patients during the second and fifth years post-transplant. BKPyV-DNAemia tended to be associated (HR 2.08, $p = 0.024$) with an increased risk of late TCMR (> 12 months of post-transplant). No independent risk factor for the development of late TCMR could be identified in patients with low immunologic risk (data not shown).

BKPyV-DNAemia (HR 2.64, p = 0.012) and a higher HLA mismatch (HR 2.46, $p = 0.044$) were independent risk factors for the development of dnDSA. Thirty-one patients (20.1%) of 154 patients developed dnDSA and/or ABMR during the observation period. The rate of dnDNA and/or

Table 3 Baseline and transplant characteristics of patients with low immunologic risk

Parameter	Entire cohort ($n=154$)	BKPyV-DNAemia ($n=48$)	No BKPyV-DNAemia ($n=106$)	*P* value
Age at KTx, years (median, IQR)	10.7 (4.9–14.3)	8.2 (3.5–13.0)	11.5 (5.6–14.5)	**0.037**
Male gender, *n* (%)	93 (60.4)	34 (70.8)	59 (55.7)	0.206
Caucasian, *n* (%)	144 (93.5)	45 (93.8)	99 (93.4)	0.737
Living donation, *n* (%)	54 (35.1)	17 (35.4)	37 (34.9)	0.868
Donor age, years (median, IQR)	36.0 (13.8–44.3)	30.0 (14.8–43.5)	36.5 (13.3–44.0)	0.884
Cold ischemia time, hours (median, IQR)	10.0 (3.0–14.1)	8.7 (2.3–15.2)	10.0 (3.0–13.6)	0.935
HLA mismatch, *n* (mean ± SD)	2.50 ± 1.2	2.29 ± 1.25	2.58 ± 1.24	0.191
HLA-DR mismatch, *n* (mean ± SD)	0.81 ± 0.63	0.81 ± 0.67	0.80 ± 0.62	0.976
Delayed graft function, n (%)	9 (5.8)	2 (4.17)	7 (6.60)	0.560
Initial eGFR, mL/min·1.73 m^2 (mean ± SD)[a]	78.5 ± 30.2	79.36 ± 25.5	78.10 ± 32.6	0.457
Initial immunosuppressive regimen[b]				
IL-2R antibody induction, *n* (%)	60 (39.0)	17 (35.4)	43 (40.6)	0.536
Maintenance immunosuppression				
TAC, *n* (%)	129 (83.8)	43 (89.6)	86 (81.1)	0.187
CSA, *n* (%)	25 (16.2)	5 (10.4)	20 (18.9)	0.187
MMF, *n* (%)	136 (88.3)	41 (85.4)	95 (89.6)	0.364
EVR, *n* (%)	10 (6.5)	4 (8.3)	6 (5.7)	0.518
AZA, *n* (%)	8 (5.2)	3 (6.3)	5 (4.7)	0.494
Steroids, *n* (%)	153 (99.4)	47 (97.9)	106 (100)	0.515
TAC/MMF, *n* (%)	115 (74.7)	38 (79.2)	77 (72.6)	0.680
TAC/EVR, *n* (%)	7 (4.5)	2 (4.2)	5 (4.7)	0.700
TAC/AZA, *n* (%)	7 (4.5)	4 (6.3)	4 (3.8)	0.459
CSA/MMF, *n* (%)	21 (13.6)	3 (6.3)	18 (17.0)	0.095
CSA/EVR, *n* (%)	3 (1.9)	2 (4.17)	1 (0.9)	0.586
CSA/AZA, *n* (%)	1 (0.6)	0	1 (0.9)	1.000
Pediatric Vasudev score (mean ± SD)[c,d]	14.4 ± 5.0	15.0 ± 5.3	14.1 ± 4.8	0.329

BKPyV BK polyomavirus, *KTx* kidney transplantation, *HLA* human leukocyte antigen, *eGFR* estimated glomerular filtration rate, *IL-2R* interleukin 2 receptor, *TAC* tacrolimus, *CSA* cyclosporine microemulsion, *MMF* mycophenolate mofetil, *EVR* everolimus, *AZA* azathioprine

[a]Defined as eGFR at 30 days of post-transplant. eGFR was calculated according to the revised Schwartz formula: eGFR = (mL/min·1.73 m^2) = 0.413 × [height (cm)/serum creatinine (mg/dL)]

[b]Until day 30 of post-transplant

[c]Defined in ref. 4, 31

[d]At 30 days of post-transplant

ABMR was significantly higher in pediatric kidney allograft recipients with BKPyV-DNAemia (16/48, 33.3%) than in those without (15/106, 14.2%, $p=0.011$). In addition, patients with BKPyV-DNAemia developed dnDSA/ABMR significantly ($p=0.010$) earlier than patients without BKPyV-DNAemia during the first 12 months of post-transplant (Fig. 3). Independent risk factors for the development of dnDSA and/or ABMR in low immunologic-risk patients were BKPyV-DNAemia (HR 2.79, $p=0.007$) and a higher HLA DR mismatch (HR 1.98, $p=0.016$) (Table 2).

Graft function deterioration, defined as an eGFR < 30 mL/min·1.73 m^2 or an eGFR decline ≥ 50% of baseline, occurred in 20 (13.0%) patients during the 5-year follow-up period. The incidence of this event (eGFR < 30 mL/min·1.73 m^2 or an eGFR decline ≥ 50% of baseline) was significantly ($p=0.005$) higher in pediatric kidney allograft recipients with BKPyV-DNAemia (13/48, 27.1%) than in those without (7/106, 6.4%, $p=0.001$). Independent risk factors for eGFR loss in low immunologic risk were BKPyV-DNAemia (HR 4.51, $p=0.001$) and TCMR (HR 5.14, $p=0.004$) (Table 2). Excluding the ten patients with TCMR during BKPyV-DNAemia from the analysis had no impact on the pattern of risk factors for graft function deterioration (Supplemental Table S2).

Discussion

The main findings of this international longitudinal cohort study of 195 pediatric kidney transplant recipients are the following: (i) BKPyV-DNAemia was significantly

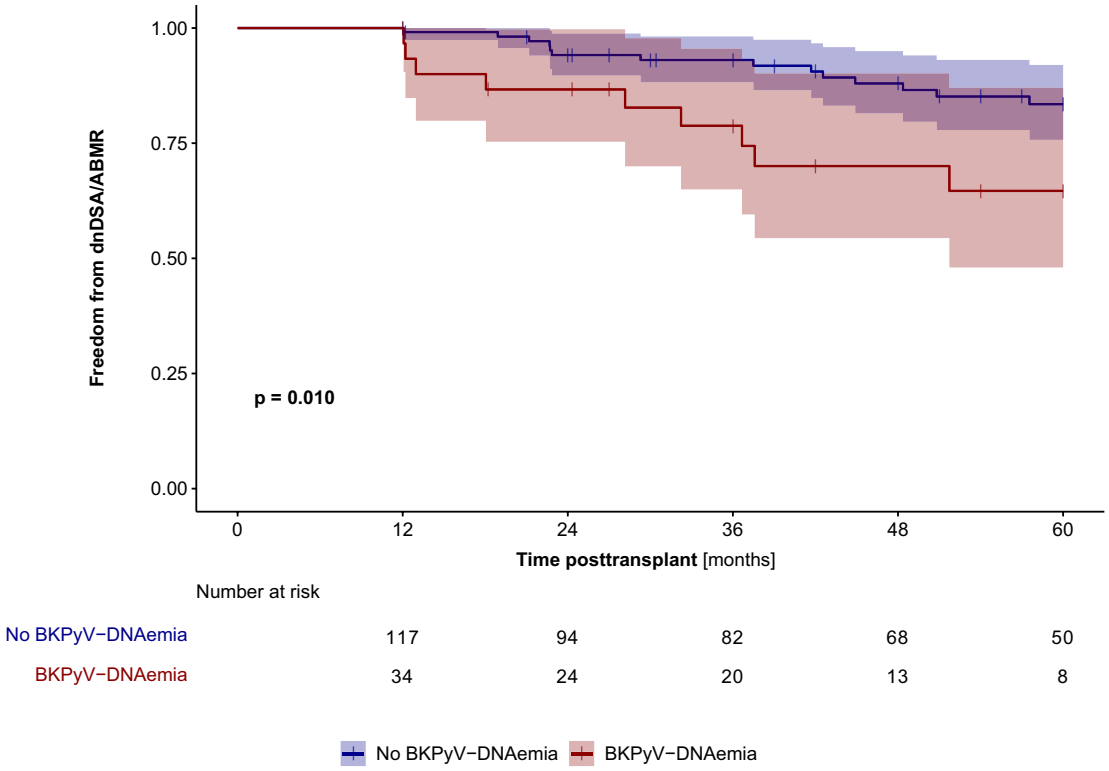


Fig. 3 Freedom from de novo DSA (dnDSA) positivity and/or antibody-mediated rejection (ABMR) in low-risk patients (n = 154) with (red line) and without (blue line) BKPyV-DNAemia during the first 12 months of post-transplant (landmark analysis). BKPyV-DNAemia was significantly associated with the development of dnDSA/ABMR (p = 0.010)

associated with a twofold increased risk of late TCMR, presumably due to reduced immunosuppressive therapy for management of BKPyV-DNAemia; (ii) patients with BKPyV-DNAemia developed dnDSA and/or ABMR more frequently and earlier than recipients without BKPyV-DNAemia (40.7% *vs*. 23.5%); (iii) BKPyV-DNAemia (HR 2.64), a higher HLA mismatch (HR 2.72), and re-transplantation (HR 6.40) were independent risk factors for dnDSA and /or ABMR; (iv) patients with BKPyV-DNAemia were significantly more likely to experience graft function deterioration than those without (25.4% *vs*. 11.0%); and (v) BKPyV-DNAemia (HR 2.73), TCMR (HR 3.87), a higher donor age (HR 1.03), and re-transplantation (HR 3.56) were found to be independent risk factors for eGFR loss. In patients with low-immunologic risk, (i) BKPyV-DNAemia was also associated with a higher rate and an earlier onset of dnDSA and/or ABMR (33.3% *vs*. 14.2%) and (ii) BKPyV-DNAemia (HR 2.74) and a higher HLA-DR mismatch (HR 1.98) were found to be independent risk factors for dnDSA and/or ABMR. In addition, (iii) graft function deterioration occurred significantly more often in patients with BKPyV-DNAemia than in those without (27.1% *vs*. 6.4%) and (iv) BKPyV-DNAemia (HR 4.51) and TCMR (HR 5.14) were significantly associated with a higher risk of eGFR loss in these patients.

This large multicenter study analyzed the risk of alloimmune responses (TCMR, dnDSA/ABMR) and graft function deterioration after reduced immunosuppression for BKPyV-DNAemia management in pediatric kidney allograft recipients. In this patient population, BKPyV-DNAemia was associated with a more than twofold risk of late (> 12 months of post-transplant) TCMR and dnDSA/ABMR development and up to 4.5-fold increased risk of graft function deterioration. Re-transplantation and a higher HLA mismatch were associated with an increased risk of dnDSA/ABMR development. Interestingly, in patients with a low immunologic risk, only the HLA *DR* mismatch but not total HLA mismatch, played a significant role in the development of dnDSA and/or ABMR.

The association of BKPyV-DNAemia and late TCMR is an interesting finding. However, one has to take into account that ten patients were diagnosed with TCMR (in the absence of SV40Ag) under ongoing BKPyV-DNAemia. The distinction between BKPyVAN and TCMR is challenging, and the diagnosis of TCMR during BKPyV-DNAemia cannot be diagnosed with certainty [35]. After excluding patients diagnosed with TCMR during BKPyV-DNAemia the association between BKPyV-DNAemia and late TCMR was no longer significant. However, the question of how to interpret interstitial nephritis in the context of BKPyV-DNAemia remains open. Two single-center, retrospective studies have

addressed the issue of alloimmune response in pediatric kidney transplant recipients with BKPyV-DNAemia [26, 27, 36]. One study found no significant effect of BKPyV-DNAemia on the rate of graft rejection, patient, or graft survival. However, this study focused primarily on the analysis of risk factors for the development of BKPyV-DNAemia rather than on the outcome of BKPyV-DNAemia management. Rejection episodes were described only as "acute" or "chronic", regardless of whether they were T cell- or antibody-mediated. No information was provided on dnDSA development or graft function deterioration [27]. Another small single-center study reported on 46 pediatric kidney allograft recipients, nine of whom had BKPyV-DNAemia. Two of these patients developed dnDSA, and one experienced ABMR. However, the small number of patients does not allow a valid statement on the risk of alloimmune reactions in this population [26].

In adult kidney allograft recipients, a number of single-center, retrospective studies have reported on the association between BKPyV-DNAemia or BKPyVAN and alloimmune responses to the graft. Our findings are consistent with most but not all of these studies in adults. Gras et al. conducted a single-center case–control study of 64 adult kidney transplant patients with biopsy-proven BKPyVAN and 64 controls [21]. The authors observed a higher rate of acute rejection episodes in recipients with BKPyVAN than in those without (19% *vs*. 3%, $p = 0.003$), a higher proportion of patients with dnDSA (MFI > 3000) (42% *vs*. 16%, $p = 0.004$), and a significantly worse kidney function in recipients with BKPyVAN. The results of that adult study support our findings in pediatric kidney transplant recipients but are limited to the fact that only patients with biopsy-proven BKPyVAN were included, but not those with BKPyV-DNAemia. Another single-center, retrospective study analyzed data from 174 adult kidney allograft recipients, 19 of whom had BKPyV-DNAemia [13]. Within 24 months after BKPyV-DNAemia detection, 79% of patients developed dnDSA, the majority of which occurred after BKPyV-DNAemia clearance. The authors concluded that post-transplant BKPyV-DNAemia and preemptive reduction of immunosuppression are associated with a higher risk of dnDSA, a finding that is consistent with our results.

In a single-center, retrospective study of 1019 adult kidney allograft recipients, Patel et al. sought to determine the association of BKPyV-DNAemia and dnDSA (MFI > 2000) [14]. One hundred and eighty-six patients had BKPyV-DNAemia, and 54 had progression to BKPyVAN. In all patients with BKPyV-DNAemia, immunosuppression was reduced to facilitate BKPyV clearance. The authors identified a higher HLA mismatch, a peak BKPyV viral load > 6 $\log_{10}$ copies/ml, and BKPyV clearance as independent risk factors for dnDSA development following BKPyV-DNAemia. These are interesting results, although it should be noted that the risk factor analysis was performed only in patients with BKPyV-DNAemia. Therefore, no statement can be made about the direct relationship between BKPyV-DNAemia and dnDSA development [14]. Another single-center, retrospective study examined risk factors for progression from low levels of BKPyV-DNAemia to adverse outcomes after reduction of immunosuppression for BKPyV management in 224 adult kidney allograft recipients [16]. Non-depleting induction at transplantation (HR 2.06), HLA mismatches > 3 (HR 2.27), and delayed graft function (HR: 4.14) were independently associated with the development of dnDSA and/or rejection in patients with BKyPVDNAemia. Because this study included only patients with BKPyV-DNAemia, no statement could be made about the relationship between BKPyV-DNAemia and dnDSA or rejection [16].

Sawinsky et al. analyzed the association between persistent BKPyV-DNAemia and dnDSA development (MFI > 800) in a single-center, retrospective study among 785 adult kidney or kidney/pancreas transplant recipients, 132 of whom developed BKPyV-DNAemia [15]. Persistent BKPyV-DNAemia did not adversely affect mid-term patient and graft survival in this cohort but was strongly associated with a twofold risk of class II dnDSA development, confirming our findings in pediatric kidney transplant recipients. Other independent risk factors for dnDSA in the adult cohort were panel reactive antibodies ≥ 30% and "acute rejection" [15]. Another single-center, retrospective study evaluated the relationship between BKPyVAN, isolated BKPyV-DNAemia, dnDSA (MFI > 1000), and the subsequent risk of ABMR in 904 adult kidney allograft recipients [17]. Thirty patients had BKPyV-DNAemia, and 43 patients had biopsy-proven BKPyVAN. BKPyVAN, but not BKPyV-DNAemia without histological findings, was a risk factor for dnDSA development in this study (HR 3.18, $p = 0.08$). In addition, BKPyVAN and dnDSA were significant predictors of ABMR and death-censored graft loss [17]. These results are partially consistent with our findings. However, in contrast to the adult study, BKPyV-DNAemia was significantly associated with dnDSA development in our pediatric population. When interpreting these results, it is important to note that in the adult study, only patients with a high BKPyV-DNAemia above 15,000 copies/ml were considered positive, whereas in our study all patients with BKPyV-DNAemia were considered positive. In addition, the authors noted that MMF was discontinued more frequently in their patients with BKPyVAN than in recipients with isolated high BKPyV-DNAemia, which may have contributed to their findings. Another explanation for the divergent results between the adult and our study may be the fact that the incidence of BKPyV-DNAemia is higher in pediatric than in adult allograft recipients, suggesting that

a higher proportion of pediatric patients have an increased risk of uncontrolled BKPyV replication, which may have an impact on the risk of alloimmune reactions [4, 37].

A recently published single-center, retrospective case–control study analyzed data from 190 adult kidney allograft recipients with BKPyV-DNAemia and 396 controls without BKPyV-DNAemia [20]. BKPyV positivity was defined as BKPyV-DNAemia > 10,000 copies/ml or BKPyVAN. dnDSA rates were higher in patients with BKPyV-DNAemia, with the majority of dnDSA detected after reduction of immunosuppression as BKPyV management, and occurred earlier post-transplant than in controls. In addition, ABMR occurred earlier in BKPyV-positive patients, although the overall rates of ABMR were comparable between cases and controls [20]. The authors concluded that their data suggest an association between reduced immunosuppression and the development of dnDSA and/or rejection, and support close monitoring for dnDSA in patients with reduced immunosuppression due to BKPyV-DNAemia [20]. Graft function and graft survival data were not reported in this study. Another retrospective, single-center study analyzed the long-term outcome of 644 Swiss adult kidney allograft recipients including 105 patients with immunosuppression reduction for BKPyV-DNAemia management [18]. In these patients, in whom the CNI dose was reduced as a first step to manage BKPyV-DNAemia, predictors of adverse outcome were a high viral load and clinical rejection after BKPyV-DNAemia clearance. A risk factor analysis for adverse outcome in the overall patient cohort, including BKPyV-DNAemia as a cofactor, was not performed in this study. In this study, only endothelialitis and ABMR were considered alloimmune reactions; and no dnDSA measurement was performed [18]. As mentioned before, the diagnosis of TCMR during ongoing BKPyV-DNAemia remains challenging. The exact mechanism of BKPyV-DNAemia-associated alloimmune reactivity remains unclear. There may be a competing mechanism for alloimmune risk: besides reduced immunosuppression, interstitial nephritis associated with BKPyVAN may itself instigate alloreactivity. This would be associated with both increased immune cell trafficking to the allograft, and increased donor cellular debris/APCs trafficking to the secondary lymphoid organs during the period of active infection. Hence, further biomarkers are needed to interpret histopathological findings in the context of BKPyV-DNAemia. A number of reports detail the time course of inflammatory markers such as CXCL10 during BK viremia, which is actually higher than what is usually seen in rejection [38–40]. Persistence of CXCL10 expression following BKV infection resolution is also associated with subsequent rejection risk [40].

A further number of retrospective studies have reported on intermediate or long-term outcomes in adult kidney allograft recipients with BKPyV-DNAemia or BKPyVAN, with varying results [19, 22–25]. However, a direct comparison of their data with those of our pediatric study is difficult. Some of these studies lacked a control cohort without BKPyV-DNAemia, or dnDSA assessment. Others evaluated "viremia" as a potential risk factor for alloimmune reactions, but did not distinguish between different viruses such as BKPyV, JC polyomavirus, cytomegalovirus, or Epstein-Barr virus.

Our study has limitations, the most important of which is the retrospective study design, which is common to registry analyses in general. Another limitation is the lack of central laboratory viral load and dnDSA assessments. However, registries reflecting the real-world scenario with heterogeneous immunosuppressive regimens and treatment protocols are potentially suitable to provide a broader view of outcome and complications, especially in small cohorts such as pediatric kidney allograft recipients. In addition, large, multicenter cohort studies, such as our present one, allow for hypothesis generation and are complementary to prospective randomized trials. Another limitation is that we cannot draw conclusions about which immunosuppressive reduction strategy is best to treat BKPyV-DNAemia and about the risk associated with dose reduction or discontinuation of specific immunosuppressants, since in most patients a combination of different approaches was used. In conclusion, our study indicates that reduction of immunosuppression for BKPyV-DNAemia treatment is associated with an increased risk of alloimmune reactivity (late TCMR and dnDSA/ABMR) in the pediatric kidney allograft population. Additional risk factors for the development of dnDSA/ABMR were found to be a higher HLA mismatch and re-transplantation. Moreover, BKPyV-DNAemia and TCMR were found to be independent predictors of graft function deterioration in pediatric kidney allograft recipients. Our data suggest that regular dnDSA screening and close monitoring of graft function in pediatric patients with BKPyV-DNAemia followed by subsequent reduction of immunosuppression are recommended. Prospective, multicenter studies are needed to confirm our results and to elucidate the exact mechanism of BKPyV-DNAemia-associated alloimmune reactivity in pediatric kidney transplant recipients.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00467-024-06501-7.

Acknowledgements This study was supported by the Peter-Stiftung. The authors would like to thank our study nurse Annette Mechler for her continuous and excellent contribution to the CERTAIN registry.

Funding Open Access funding enabled and organized by Projekt DEAL. The authors gratefully acknowledge the funding of the CERTAIN Registry by a grant from the Dietmar Hopp Stiftung, the European Society for Pediatric Nephrology (ESPN), the German Society for Pediatric Nephrology (GPN), and by grants from the pharmaceutical companies Astellas and Novartis, and Takeda.

Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors of this manuscript have conflicts of interest to disclose. Alexander Fichtner received travel grants from Astellas and Novartis. Lutz T. Weber received a research grant from Chiesi. Hans H. Hirsch reported grants from Moderna, consulting fees of AlCuris, Allovir, Moderna, VeraTx, and Roche, and speaker honoraria by VeraTx, Takeda, Biotest, and Gilead. Burkhard Tönshoff received research grants from Novartis, Astellas, and Chiesi, and consulting fees from Bristol-Myers Squibb, CSL Behring Biotherapies for Life, Vifor, and Chiesi. Britta Höcker received consulting fees from GlaxoSmithKline. Jeremy Schmidt, Caner Süsal, Andrea Carraro, Jun Oh, Matthias Zirngibl, Sabine König, Isabella Guzzo, Atif Awan, Kai Krupka, and Paul Schnitzler have no conflicts of interest.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

References

1. Hirsch HH, Randhawa PS, AST Infectious Diseases Community of Practice (2019) BK polyomavirus in solid organ transplantation-guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transplant 33:e13528. https://doi.org/10.1111/ctr.13528
2. Ginevri F, De Santis R, Comoli P, Pastorino N et al (2003) Polyomavirus BK infection in pediatric kidney-allograft recipients: a single-center analysis of incidence, risk factors, and novel therapeutic approaches. Transplantation 75:1266–1270. https://doi.org/10.1097/01.TP.0000061767.32870.72
3. Schmidt T, Adam C, Hirsch HH, Janssen MWW et al (2014) BK polyomavirus-specific cellular immune responses are age-dependent and strongly correlate with phases of virus replication. Am J Transplant 14:1334–1345. https://doi.org/10.1111/ajt.12689
4. Höcker B, Schneble L, Murer L, Carraro A et al (2019) Epidemiology of and risk factors for BK polyomavirus replication and nephropathy in pediatric renal transplant recipients: an international CERTAIN registry study. Transplantation 103:1224–1233. https://doi.org/10.1097/TP.0000000000002414
5. Smith JM, Dharnidharka VR, Talley L, Martz K, McDonald RA (2007) BK virus nephropathy in pediatric renal transplant recipients: an analysis of the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) registry. Clin J Am Soc Nephrol 2:1037–1042. https://doi.org/10.2215/CJN.04051206
6. Araya CE, Garin EH, Neiberger RE, Dharnidharka VR (2010) Leflunomide therapy for BK virus allograft nephropathy in pediatric and young adult kidney transplant recipients. Pediatr Transplant 14:145–150. https://doi.org/10.1111/j.1399-3046.2009.01183
7. Araya CE, Lew JF, Fennell RS, Neiberger RE, Dharnidharka VR (2008) Intermediate dose cidofovir does not cause additive nephrotoxicity in BK virus allograft nephropathy. Pediatr Transplant 12:790–795. https://doi.org/10.1111/j.1399-3046.2008.00937
8. Araya CE, Lew CF, Fennell RS, Neiberger RE, Dharnidharka VR (2006) Intermediate-dose cidofovir without probenecid in the treatment of BK virus allograft nephropathy. Pediatr Transplant 10:32–37. https://doi.org/10.1111/j.1399-3046.2005.00391
9. Santeusanio AD, Lukens BE, Eun J (2017) Antiviral treatment of BK virus viremia after kidney transplantation. Am J Health Syst Pharm 74:2037–2045. https://doi.org/10.2146/ajhp160585
10. Johnston O, Jaswal D, Gill JS, Doucette S, Fergusson DA, Knoll GA (2010) Treatment of polyomavirus infection in kidney transplant recipients: a systematic review. Transplantation 89:1057–1070. https://doi.org/10.1097/TP.0b013e3181d0e15e
11. Mallat SG, Tanios BY, Itani HS, Lotfi T et al (2017) CMV and BKPyV infections in renal transplant recipients receiving an mTOR inhibitor-based regimen versus a CNI-based regimen: a systematic review and meta-analysis of randomized, controlled trials. Clin J Am Soc Nephrol 12:1321–1336. https://doi.org/10.2215/CJN.13221216
12. Everly MJ, Briley KP, Haisch CE, Dieplinger G et al (2017) Racial differences in incident de novo donor-specific anti-HLA antibody among primary renal allograft recipients: results from a single center cohort study. Transpl Int 30:566–578. https://doi.org/10.1111/tri.12937
13. Dieplinger G, Everly MJ, Briley KP, Haisch CE et al (2015) Onset and progression of de novo donor-specific anti-human leukocyte antigen antibodies after BK polyomavirus and preemptive immunosuppression reduction. Transpl Infect Dis 17:848–858. https://doi.org/10.1111/tid.12467
14. Patel SJ, Kuten SA, Knight RJ, Graviss EA et al (2016) Incidence and factors associated with de novo DSA after BK viremia in renal transplant recipients. Clin Transpl 32:103–109
15. Sawinski D, Forde KA, Trofe-Clark J, Patel P et al (2015) Persistent BK viremia does not increase intermediate-term graft loss but is associated with de novo donor-specific antibodies. J Am Soc Nephrol 26:966–975. https://doi.org/10.1681/ASN.2014010119
16. Kharel A, Djamali A, Jorgenson MR, Alzoubi B et al (2021) Risk factors for progression from low level BK DNAemia to unfavorable outcomes after BK management via immunosuppressive reduction. Transpl Infect Dis 23:e13561. https://doi.org/10.1111/tid.13561
17. Cheungpasitporn W, Kremers WK, Lorenz E, Amer H et al (2018) De novo donor-specific antibody following BK nephropathy: the incidence and association with antibody-mediated rejection. Clin Transplant 32:e13194. https://doi.org/10.1111/ctr.13194
18. Bischof N, Hirsch HH, Wehmeier C, Amico P et al (2019) Reducing calcineurin inhibitor first for treating BK polyomavirus replication after kidney transplantation: long-term outcomes. Nephrol Dial Transplant 34:1240–1250. https://doi.org/10.1093/ndt/gfy346
19. Elfadawy N, Flechner SM, Schold JD, Srinivas TR et al (2014) Transient versus persistent BK viremia and long-term outcomes after kidney and kidney-pancreas transplantation. Clin J Am Soc Nephrol 9:553–561. https://doi.org/10.2215/CJN.08420813

20. Hod-Dvorai R, Lee R, Muluhngwi P, Raijmakers M et al (2023) Development of de novo donor-specific antibodies in renal transplant recipients with BK viremia managed with immunosuppression reduction. Transpl Infect Dis 25:e13993. https://doi.org/10.1111/tid.13993
21. Gras J, Le Flécher A, Dupont A, Vérine J et al (2023) Characteristics, risk factors and outcome of BKV nephropathy in kidney transplant recipients: a case-control study. BMC Infect Dis 23:74. https://doi.org/10.1186/s12879-023-08043-z
22. Schinstock CA, Dadhania DM, Everly MJ, Smith B et al (2019) Factors at de novo donor-specific antibody initial detection associated with allograft loss: a multicenter study. Transpl Int 32:502–515. https://doi.org/10.1111/tri.13395
23. Seifert ME, Gunasekaran M, Horwedel TA, Daloul R et al (2017) Polyomavirus reactivation and immune responses to kidney-specific self-antigens in transplantation. J Am Soc Nephrol 28:1314–1325. https://doi.org/10.1681/ASN.2016030285
24. Mohamed M, Parajuli S, Muth B, Astor BC et al (2016) In kidney transplant recipients with BK polyomavirus infection, early BK nephropathy, microvascular inflammation, and serum creatinine are risk factors for graft loss. Transpl Infect Dis 18:361–371. https://doi.org/10.1111/tid.12530
25. Naef B, Nilsson J, Wuethrich RP, Mueller TF, Schachtner T (2021) Intravenous immunoglobulins do not prove beneficial to reduce alloimmunity among kidney transplant recipients with BKV-associated nephropathy. Transpl Int 34:1481–1493. https://doi.org/10.1111/tri.13882
26. Miettinen J, Lautenschlager I, Weissbach F, Wernli M et al (2019) BK polyomavirus viremia and antibody responses of pediatric kidney transplant recipients in Finland. Pediatr Transplant 23:e13324. https://doi.org/10.1111/petr.13324
27. Schoephoerster J, Jensen C, Jackson S, Plautz E et al (2023) BK DNAemia in pediatric kidney transplant recipients: predictors and outcomes. Pediatr Transplant 27:e14372. https://doi.org/10.1111/petr.14372
28. Tönshoff B, Krupka K, Köster L, Fichtner A, Pape L, Höcker B (2015) CERTAIN registry. Der Nephrologe 10:480–487
29. Plotnicki L, Kohl CD, Höcker B, Krupka K et al (2013) The CERTAIN registry: a novel, web-based registry and research platform for pediatric renal transplantation in Europe. Transplant Proc 45:1414–1417. https://doi.org/10.1016/j.transproceed.2013.01.007
30. Loupy A, Haas M, Roufosse C, Naesens M et al (2020) The Banff 2019 kidney meeting report (I): updates on and clarification of criteria for T cell- and antibody-mediated rejection. Am J Transplant 20:2318–2331. https://doi.org/10.1111/ajt.15898
31. Höcker B, Fickenscher H, Delecluse HJ, Böhm S et al (2013) Epidemiology and morbidity of Epstein-Barr virus infection in pediatric renal transplant recipients: a multicenter, prospective study. Clin Infect Dis 56:84–92. https://doi.org/10.1093/cid/cis823
32. Tambur AR, Campbell P, Claas FH, Feng S et al (2018) Sensitization in transplantation: assessment of risk (STAR) 2017 Working Group Meeting Report. Am J Transplant 18:1604–1614. https://doi.org/10.1111/ajt.14752
33. Schwartz GJ, Muñoz A, Schneider MF, Mak RH et al (2009) New equations to estimate GFR in children with CKD. J Am Soc Nephrol 20:629–637. https://doi.org/10.1681/ASN.2008030287
34. Schwartz GJ, Schneider MF, Maier PS, Moxey-Mims M et al (2012) Improved equations estimating GFR in children with chronic kidney disease using an immunonephelometric determination of cystatin C. Kidney Int 82:445–453. https://doi.org/10.1038/ki.2012.169
35. Kotton CN, Kamar N, Wojciechowski D, Eder M et al (2024) The second international consensus guidelines on the management of BK polyomavirus in kidney transplantation. Transplantation. https://doi.org/10.1097/TP.0000000000004976
36. Aldieri A, Chandran M, Matossian D, Hariprasad A et al (2024) Leflunomide as adjunct therapy for BK viremia management in pediatric kidney transplant recipients. Pediatr Transplant 28:e14724. https://doi.org/10.1111/petr.14724
37. Höcker B, Tönshoff B (2019) Polyomavirusinfektionen bei pädiatrischen Nierentransplantat-empfängern. Nephrologe 14:199–205
38. Parajuli S, Mandelbrot D (2023) Urine CXCL10 levels as a predictor for various phases of BKPyV replication among kidney transplant recipients: utility and clinical implementation. Transplantation 107:2460–2461. https://doi.org/10.1097/TP.0000000000004713
39. Haller J, Diebold M, Leuzinger K, Wehmeier C et al (2023) Urine CXCL10 to assess BK polyomavirus replication after kidney transplantation. Transplantation 107:2568–2574. https://doi.org/10.1097/TP.0000000000004712
40. Barrett-Chan E, Wang L, Bone J, Thachil E, Vytlingam K, Blydt-Hansen T (2024) Optimizing the approach to monitoring allograft inflammation using serial urinary CXCL10/creatinine testing in pediatric kidney transplant recipients. Pediatr Transplant 28:e14718. https://doi.org/10.1111/petr.14718

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Authors and Affiliations

Alexander Fichtner[1] · Jeremy Schmidt[1] · Caner Süsal[2,3] · Andrea Carraro[4] · Jun Oh[5] · Matthias Zirngibl[6] · Sabine König[7] · Isabella Guzzo[8] · Lutz T. Weber[9] · Atif Awan[10] · Kai Krupka[1] · Paul Schnitzler[11] · Hans H. Hirsch[12,13] · Burkhard Tönshoff[1] · Britta Höcker[1]

✉ Britta Höcker
britta.hoecker@med.uni-heidelberg.de

1 Heidelberg University, Medical Faculty Heidelberg, Department of Pediatrics I, University Children's Hospital, Im Neuenheimer Feld 430, Heidelberg 69120, Germany

2 Heidelberg University, Medical Faculty Heidelberg, Department of Transplantation Immunology, Institute of Immunology, Heidelberg, Germany

3 Transplant Immunology Research Center of Excellence, Koç University, Istanbul, Turkey

4 Pediatric Nephrology, Dialysis and Transplantation Unit, Department of Woman's and Child's Health, University Hospital of Padova, Via Giustiniani 3, 35128 Padua, Italy

5 Department of Pediatric Nephrology, University Children's Hospital, Martinistr. 52, 20246 Hamburg, Germany

6 University Children's Hospital, Hoppe-Seyler-Str. 1, 72076 Tübingen, Germany

7 Department of General Pediatrics, University Children's Hospital Münster, Waldeyerstraße 22, 48149 Münster, Germany

8 Pediatric Nephrology and Renal Transplant Unit, Bambino Gesù Children's Hospital–IRCCS, Piazza S. Onofrio 4, 00165 Rome, Italy

9 Pediatric Nephrology, Children's and Adolescents' Hospital, University Hospital of Cologne, Faculty of Medicine, University of Cologne, Kerpener Street 62, 50937 Cologne, Germany

10 Temple Street Children's University Hospital, Dublin 1, Ireland

11 Department of Infectious Diseases, Virology, Heidelberg University, Medical Faculty Heidelberg, Im Neuenheimer Feld 324, Heidelberg 69120, Germany

12 Transplantation & Clinical Virology, Department Biomedicine, University of Basel, Petersplatz 10, 4009 Basel, Switzerland

13 Infectious Diseases & Hospital Epidemiology, University Hospital Basel, Petersgraben 4, 4031 Basel, Switzerland