BK virus infection and outcome following kidney transplantation in childhood

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BK virus associated nephropathy (BKN) is an important cause of kidney allograft failure. In a cohort of paediatric kidney transplant recipients, we aimed to understand the incidence and clinical outcome associated with BKN, as well as identify risk factors for BKN and BK viraemia development. We retrospectively analysed all patients who received a kidney transplant and received follow up care in our centre between 2009–2019. Among 106 patients included in the study (mean follow up 4.5 years), 32/106 (30.2%) patients experienced BK viraemia. The incidence of BKN was 7/106 (6.6%). The median time of BK viraemia development post-transplant was 279.5 days compared to 90.0 days for BKN. Development of BKN was associated with younger age at transplantation (p = 0.013). Development of BK viraemia was associated with negative recipient serology for cytomegalovirus (CMV) at time of transplantation (p = 0.012) and a higher net level of immunosuppression (p = 0.039). There was no difference in graft function at latest follow up between those who experienced BKN and those without BKN. This study demonstrates that BK virus infection is associated with younger age at transplantation, CMV negative recipient serostatus and higher levels of immunosuppression. Judicious monitoring of BK viraemia in paediatric transplant recipients, coupled with timely clinical intervention can result in similar long-term outcomes for BKN patients compared to controls.

BK virus (BKPyV) is a member of the Polyomaviridae family of double-stranded DNA viruses1. Primary BKPyV infection is mainly asymptomatic and occurs predominantly before adolescence, with an IgG seroprevalence >90% in 5–9 year old healthy children. Seroprevalence rates in later life demonstrate an age-dependent decline with 68% of 60–69 year olds showing IgG positivity2. Peripheral blood mononuclear cells disseminate BKPyV to the urinary tract where the virus establishes a persistent non-replicative latent phase in renal tubular epithelial cells and urothelium3,4. Periodic BKPyV reactivation occurs, with asymptomatic urinary shedding seen in 7% of healthy adults5.

In kidney allograft recipients, active replication of BKPyV can lead to BKPyV-associated nephropathy (BKN) and subsequent graft dysfunction and premature loss6. The emergence of BKN in the last decade of the twentieth century coincided with the introduction of potent immunosuppressive agents such as tacrolimus and mycophenolate mofetil (MMF), leading to the proposal that a higher level of immunosuppression is a risk factor for the development of BKN7,8. BKPyV viraemia precedes the onset of BKN, and polymerase-chain-reaction (PCR) assays of plasma are a specific and sensitive method to detect early nephropathy9. Before recognition of the necessity to identify and treat BKN in a timely manner, graft loss rates as high as 67% were documented in the adult population10.

Anti-viral agents have demonstrated minimal or no efficacy in clearing BKPyV11–13, and treatment involves reducing immunosuppressive therapy to restore the capability of the host immune system to control BKPyV replication and prevent progression to BKN14. Levels of BKPyV-specific IgG antibodies and T-cells increase following a reduction in immunosuppression and peak at the time of BKPyV viraemia resolution15.

In the paediatric kidney transplant population, rates of BKPyV viraemia range from 18–37% and BKN is identified in 0–16% of patients12,15–23. In a case series of 32 patients under the age of 20 years with BKN, 3 (9%) of allografts were lost6. Reported risk factors for the development of BKN in the paediatric population include allograft recipient BKPyV seronegativity at time of transplantation20,23, zero human leukocyte antigens (HLA) -A and -DR mismatches between transplant donor and recipient22, increased levels of immunosuppression,21

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younger age of recipient at transplantation\(^2\), and a tacrolimus- compared to ciclosporin- based immunosuppression regimen\(^2\). A recent study in adult kidney transplant recipients suggested prophylactic use of the anticytomegalovirus (CMV) agent valganciclovir may be associated with an increased risk of BKN\(^2\).

In this single-centre study, we report our experience of BKN in a paediatric transplant recipient population over a 10-year period, with patients predominantly receiving a steroid-sparing immunosuppressive regimen\(^2\). Specific aims of the study were to: (1) evaluate rates of BKPyV viraemia and BVN in this population; (2) understand the morbidity associated with BKPyV viraemia and BKN; and (3) identify risk factors for the development of BKPyV viraemia and BKN.

### Results

#### Study population.

A total of 106 patients met the requirements for inclusion in the study, with a mean follow up time of 54.3 months. There were 7 graft failures (mean time in months post-transplant: 44.0 months, range 18–70 months) and 2 deaths (see Supplementary Table S1). There were no graft losses or deaths in BKN\(^{Hi/B+}\) patients (Table 1). 99/106 patients received the steroid-sparing TWIST immunosuppressive regimen. 7/106 patients received a non-TWIST immunosuppression regimen (reasons including enrolment in research trials and transplant occurring before TWIST became standard local protocol). Characteristics for the whole cohort are provided in Supplementary Tables S2, S3 and S4.

#### Incidence of BKN.

There were 41 episodes of BK viraemia in 32/106 patients (30.2%). 2/106 patients (1.9%) experienced an episode of BKN\(^{B+}\), and a further 5/106 (4.7%) patients experienced an episode of BKN\(^{Hi/B+}\). Therefore, the incidence of BKN\(^{Hi/B+}\) was 7/106 (6.6%). 25/106 patients (23.6%) experienced an episode of BKN\(^{Low}\) without an episode of BKN\(^{Hi/B+}\) at any point post-transplantation.

#### Timing of episodes.

The mean (median) time of viraemia onset post-transplant in the 34 episodes of BKN\(^{Low}\) was 508.4 (279.5) days compared to 234.3 (90.0) days for BKN\(^{Hi/B+}\) (\(p = 0.199\)) (Fig. 1a and Supplementary Table S5). The range of time of onset of viraemia post-transplant was 19–1775 days for BKN\(^{Low}\) episodes and 33–656 days for BKN\(^{Hi/B+}\). 23.5% of BKN\(^{Low}\) episodes occurred more than 2 years post transplant. In contrast, all episodes of BKN\(^{Hi/B+}\) occurred within the first 2 years following transplantation.

#### Analysis of risk factors.

Univariate analysis was performed to assess potential risk factors for the development of BKPyV viraemia and BKN. Age at transplant was significantly different between the 3 groups (\(p = 0.0369\)) (Table 1). Bonferroni’s post-test was used to compare groups and there was a significant difference in age at transplantation between no-BKV patients (mean 11.2 years) compared to BKN\(^{Hi/B+}\) patients (mean 6.2 years) (\(p = 0.013\), adjusted critical value \(\alpha_{\text{Bonferroni}} = 0.0167\) for three group comparison). There was no difference between age at transplantation between no-BKV patients and BKN\(^{Low}\) patients (mean 10.2 years) (\(p = 0.363\)).

CMV serology status of allograft recipients was also significantly different between the groups (\(p = 0.012\)) (Table 2). BKN\(^{Low}\) patients were less likely to have recorded positive CMV serology at time of transplantation.

| Characteristic                        | No-BKV (n = 74) | BKN\(^{Low}\) (n = 25) | BKN\(^{Hi/B+}\) (n = 7) | \(p\) value |
|--------------------------------------|----------------|-------------------------|--------------------------|-------------|
| Female                               | 24/74 (32.4%) | 9/25 (36.0%)            | 2/7 (28.6%)              | 0.939       |
| Male                                 | 50/74 (67.6%) | 16/25 (64.0%)           | 5/7 (71.4%)              |             |
| Age at transplant (years)            |               | 11.2                    | 10.2                     | 6.2         | 0.0369 |
| Ethnicity: White British*            | 45/68 (66.2%) | 17/25 (68.0%)           | 5/7 (71.4%)              | 1.000       |
| Living transplant donor              | 43/74 (58.1%) | 18/25 (72.0%)           | 6/7 (85.7%)              | 0.228       |
| Cold ischaemia time (minutes)        | 345.2         | 235.6                   | 143.9                    | 0.218       |
| Steroid-free regimen at latest follow up | 44/74 (59.5%) | 11/25 (44.0%)           | 4/7 (57.1%)              | 0.448       |
| MMF part of regimen at latest follow up | 55/74 (74.3%) | 16/25 (64.0%)           | 5/7 (71.4%)              | 0.543       |
| Exposure to anti-CMV therapy         | 24/74 (32.4)  | 10/25 (40.0%)           | 3/7 (42.9%)              | 0.735       |
| BPAR                                 | 21/74 (28.4%) | 6/25 (24.0%)            | 2/7 (28.6%)              | 0.933       |
| Graft failure                        | 7/74 (9.5%)   | 1/25 (4.0%)             | 0/7 (0.0%)               | 0.802       |
| Death                                | 2/74 (2.7%)   | 0/25 (0.0%)             | 0/7 (0.0%)               | 1.000       |
| Length of follow up (months)         | 55.8          | 48.0                    | 40.1                     | 0.453       |

Table 1. Univariate analysis of patient cohort characteristics. *Data not available for six patients. BPAR = biopsy proven acute rejection.
Figure 1. Characteristics of BKPyPV viraemia episodes. (a) Time of onset of viraemia episodes post-transplant ($p = 0.199$, Mann–Whitney U test). Red line indicates mean value for each group. (b) Cumulative risk of developing BKPyPV viraemia over time (curves compared using log-rank / Mantel-Cox test). (c) Violin plot comparing length of viraemia episodes between groups ($p = 0.265$, Mann–Whitney U test). Quartiles are plotted with median value in red. ns = not significant.

Figure 2. Incidence of BKN\textsubscript{Low}, BKN\textsubscript{B+} and BKN\textsubscript{Hi} in years 1–5 post transplantation.

Table 2. Univariate analysis of CMV serostatus of transplant donor and recipient.
than no-BKV (27/74; 36.5%) and BKNHi/B+ (3/7, 42.9%) patients. There was no difference in exposure to anti-CMV therapy between patient subgroups (Table 1 and Supplementary Table S7).

No differences between patient subgroups were identified for the following characteristics: sex, cold ischaemia time, ethnic background, frequency of BPAR, use of steroids/MMF, source of graft donor (living/cadaveric) and HLA mismatch status (Table 1 and Supplementary Table S8).

Multinomial logistic analysis confirmed the univariate analysis findings of CMV recipient serostatus and age at time of transplant being independently predictive of BKN and BKPyV viraemia. Additionally, age and CMV serostatus in the same model are predictive of BKN/ BKPyV viraemia ($p = 0.002$) (Table 3).

Immunosuppression. All (7/7) episodes of BKNHi/B+ elicited a reduction in immunosuppression by the treating clinician compared to 13/34 (38.2%) of episodes of BKNLow (Supplementary Table S9). However, when the decision to reduce immunosuppression was made, there was no significant difference between the size of reduction between BKNLow (mean reduction in paediatric Vasudev score -23.0%) and BKNHi/B+ (mean reduction in paediatric Vasudev score -22.2%) (Fig. 3a,b).

To understand how the total level of immunosuppression varied for patients across their post-transplant clinical course, a paediatric Vasudev score was calculated for all patients at latest follow up and, for relevant patients, at time of BKPyV viraemia onset. Additionally we quantified the level of immunosuppression for

| Factor                        | $p$ value of reduced model | $p$ value of final model | BKNLow, status | BKNHi/B+, status |
|-------------------------------|-----------------------------|--------------------------|----------------|------------------|
| Age at transplant             | 0.027                       | 0.002                    | 0.975          | 0.889 to 1.070   |
| CMV serostatus of recipient   | 0.009                       | 0.002                    | 0.157          | 0.034 to 0.723   |

Table 3. Multinomial Logistic Regression Analysis. *Log Likelihood tests; **OR: odds ratio; *CI: confidence interval for odds ratio; #Reference category is No-BKV.

Figure 3. Change in net immunosuppression over time. (a) Percentage change in paediatric immunosuppression Vasudev score during episodes of BKPyV viraemia ($p = 0.588$, Mann–Whitney U test). (b) Absolute change in paediatric immunosuppression Vasudev score during episodes of BKPyV viraemia ($p > 0.999$, Mann–Whitney U test). (c) Mean paediatric Vasudev immunosuppression score at latest follow up, at BKPyV viraemia diagnosis and at 462 days post-transplantation in no-BKV group. Groups compared using one way ANOVA followed by Tukey’s test. ns = not significant ($p = 0.996$), ***$p = 0.0115$, **$p = 0.0390$, *$p = 0.0391$. 

(2/25, 8.0%) than no-BKV (27/74, 36.5%) and BKNHi/B+ (3/7, 42.9%) patients. There was no difference in exposure to anti-CMV therapy between patient sub-groups (Table 1 and Supplementary Table S7).

No differences between patient subgroups were identified for the following characteristics: sex, cold ischaemia time, ethnic background, frequency of BPAR, use of steroids/MMF, source of graft donor (living/cadaveric) and HLA mismatch status (Table 1 and Supplementary Table S8).

Multinomial logistic analysis confirmed the univariate analysis findings of CMV recipient serostatus and age at time of transplant being independently predictive of BKN and BKPyV viraemia. Additionally, age and CMV serostatus in the same model are predictive of BKN/ BKPyV viraemia ($p = 0.002$) (Table 3).
no-BKV patients at the mean time BKVAll patients developed viraemia post-transplant (462 days). This allowed us to analyse no-BKV and BKVAll patients at comparable points in their clinical course.

There was no significant difference in paediatric Vasudev score at latest follow up between no-BKV patients (mean 4.4 units) compared to BKVAll patients (mean 4.7 units) (Fig. 3c). However, the level of immunosuppression was significantly higher for BKVAll patients at time of BKPyV viraemia diagnosis (mean 6.5 units) compared to latest follow-up ($p = 0.012$). Furthermore, immunosuppression level in no-BKV patients at 462 days post-transplantation (mean 5.2 units) was significantly lower than for BKVAll patients at BKPyV viraemia diagnosis ($p = 0.0390$). This shows that patients who developed BKPyV viraemia were exposed to a higher level of immunosuppression at time of diagnosis than patients without BKPyV viraemia.

To understand if increases in immunosuppression following an episode of acute rejection may explain the higher paediatric Vasudev score recorded for BKVAll patients, we examined whether BKPyV viraemia or acute rejection occurred first for each relevant patient. There were 8 episodes of BPAR among BKVAll patients: in 4/8 episodes rejection occurred before BKPyV viraemia and in 4/8 episodes BKPyV viraemia occurred before rejection. 2/2 BKNb+ patients experienced an episode of acute rejection: in both instances BKNb occurred before acute rejection.

Effect on kidney function. There was no significant difference in eCrCl between patient sub-groups at latest follow up or significant difference in the eCrCl percentage change from baseline to latest follow up between patient sub-groups (Fig. 4a,b). To analyse changes in kidney function during periods of viraemia, the eCrCl at BKPyV viraemia diagnosis was compared to the lowest eCrCl during the period of viraemia for each patient and a percentage change was calculated. BKNLow patients showed a mean eCrCl change of $-0.2\%$, while BKNb+ patients showed a mean eCrCl change of $-10.0\%$ (Fig. 4c). However, there was no significant difference between the eCrCl at BKPyV viraemia diagnosis and the average eCrCl reading during viraemia for either BKNLow or BKNb+ patients (Supplementary Figure S1). A representative plot of plasma viral load and eCrCl of a patient with BKNb+ over time. Green arrows indicate points at which immunosuppressive therapy was reduced.

Discussion

The salient findings of this study involving 106 paediatric kidney transplant recipients are as follows: (1) 2/106 individuals experienced BKNb+, and 5/106 patients developed BKNb+ giving an overall BKN incidence of 7/106 (6.6%); (2) 30.2% patients experienced BKPyV viraemia; (3) the incidences of BKNLow, BKNb, and BKNb+ were highest during the first year post-transplant; (4) 23.5% of BKNLow episodes occurred after 2 years post-transplantation; (5) there was no significant difference in long-term graft function between patients experiencing BKPyV
viraemia/BKN and no-BK controls; (6) younger age at transplantation, CMV negative serology of the allograft recipient at time of transplantation, and a higher level of immunosuppression were associated with an increased risk of BKN/ BKPyV viraemia development.

Our incidence of BKPyV viraemia (1.9%) is slightly lower than rates of 3.5–4.5% recorded in previous studies\(^20–22\). We found similar levels of BKPyV viraemia to a recent European multicentre study (30.2% vs. 36.7%), but lower were recorded. Immunosuppression regimens for each patient were documented at latest follow up, and during transplantation and at 6 monthly intervals thereafter. All plasma BKPyV quantification and histology results received more than one transplant, the first transplant was evaluated.

Calculating using the standard Schwartz formula (k = 40, as per local protocol)\(^28\). All SCr readings during periods were recorded for each serum creatinine (SCr) reading, to allow the estimated creatinine clearance (eCrCl) to be calculated. This approach results in comparable graft function and survival outcomes between patients developed BKPyV viraemia in seropositive patients. Following a recent report linking prophylactic valganciclovir use with an increased risk of BKN\(^24\), we investigated whether anti-CMV therapy (routinely prescribed in CMV negative individuals) was associated with an increased risk of BKPyV replication in our cohort. However, we found no evidence to support this (Table 1 and Supplementary Table S7). CMV seropositivity rapidly increases with age during childhood in a similar manner to rates of BKPyV seropositivity\(^27\). It is therefore possible that seronegative CMV individuals are more likely to also be BKPyV seronegative, and therefore at heightened risk of uncontrolled viral replication during primary BKPyV infection. However, due to the retrospective nature of the study, this conjecture cannot be confirmed.

Our study design. This is a retrospective cohort analysis of patients receiving a kidney transplant at the Royal Manchester Children's Hospital (RMCH) (UK). Case notes were reviewed from June 2009 to January 2019 and patients who met the following requirements were included in the study: (1) Aged < 19 years at time of transplantation; (2) a minimum of 12 months follow-up data; and (3) transplant performed at RMCH. For patients who received more than one transplant, the first transplant was evaluated.

Clinical and serological data were collected at time of transplant and at months 1, 3, 6, 9, 12 months post-transplantation and at 6 monthly intervals thereafter. All plasma BKPyV quantification and histology results were recorded. Immunosuppression regimens for each patient were documented at latest follow up, and during BKPyV viraemia episodes for relevant patients. Contemporaneous patient height and weight results were recorded for each serum creatinine (SCr) reading, to allow the estimated creatinine clearance (eCrCl) to be calculated using the standard Schwartz formula (k = 40, as per local protocol)\(^29\). All SCr readings during periods of BKPyV viraemia were recorded. The study protocol was reviewed by the Clinical Trial Management Department (Manchester University NHS Foundation Trust) who waived ethical approval for this study involving the retrospective collection of anonymised data. They concluded that informed consent was not required from
study participants. The study was performed in accordance with Manchester University NHS Foundation Trust guidelines. No patient identifiable data was recorded.

**BKPyV surveillance and immunosuppression regimen.** Plasma BKPyV monitoring is performed in all kidney transplant recipients every month during the first year post-transplantation and on an annual basis thereafter using a TaqMan PCR-based approach. Monitoring is performed more frequently at the treating clinician’s discretion.

The standard local immunosuppression approach is the steroid-sparing (TWIST) protocol23. Briefly, this involves induction therapy with the interleukin 2 receptor monoclonal antibody antagonist, basiliximab, on day 0 and day 4 post transplantation, coupled with a rapidly weaning course of prednisolone which is discontinued on day 5. Long-term immunosuppression is provided by tacrolimus and MMF. The net immunosuppressive load at different time points for each patient was quantified using the paediatric Vasudev score28. This score provides an estimation of the overall immunosuppressive load by integrating the immunosuppressant types, doses and body surface area of each patient. For example, a patient administered 1.2 mg/m² per day of tacrolimus (equating to a paediatric Vasudev score of 1 unit) and 580 mg/m² per day of MMF (equating to a paediatric Vasudev score of 2 units), would have a total paediatric Vasudev score of 3 units.

**Definitions.** Patients with no recorded positive BKPyV plasma result or histological evidence of BKN were designated as ‘no-BKV’. Patients with any recordable level of BKPyV viraemia at any time during study follow-up were designated as ‘BKVAIq’. The BKVAIq group was subdivided into three groups: (1) those with biopsy-proven BKN (‘BKNIq’); (2) those with presumptive BKN (‘BKNIq’i) without histological evidence of BKN. BKNIq is defined as a sustained (> 3 week) high-level viraemia (> 10⁴ copies/mL), as per international recommendations21,22; and (3) patients with BKPyV viraemia but not meeting the requirements for either BKNIq or BKNIq (‘BKNIq/B+’), were designated as having low-level viraemia (‘BKNIq’).

The length of viraemia for each episode was defined as the length of time from the first positive BKPyV plasma viraemia result until plasma levels were again undetectable. Baseline eCrCl was defined as the highest eCrCl recorded during the first year following transplantation. Graft failure was defined as the requirement to return to dialysis after the first week post-transplantation.

**Statistical analysis.** Univariate analysis of risk factors was performed using Fisher’s exact test and chi-squared test for correlation (for categorical variables) and one-way analysis of variance (ANOVA) with Bonferroni’s post-hoc test (for quantitative variables). Analysis of clinical outcomes was performed using the non-parametric Mann–Whitney U test or one-way ANOVA with Tukey’s test, as appropriate.

**Multinomial analysis.** A multinomial logistic regression analysis was used to predict the BKN development. The following variables were considered for the model: gender, ethnicity, age at transplant, cold ischaemia time, biopsy-proven acute rejection (BPAR), source of allograft (cadaveric/living), use of steroid-free regimen at latest follow-up, use of MMF at latest follow-up, exposure to anti-CMV therapy, HLA mismatch, recipient CMV status, donor CMV status. The analysis was performed in IBM SPSS Statistics Version 26. A parsimonious model was developed by using forward selection method. The final model consisted of one factor: CMV serostatus of recipient and one covariate: age at transplant.

Received: 10 November 2020; Accepted: 14 January 2021
Published online: 28 January 2021

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**Acknowledgements**
We thank Prof. Rachel Lennon and Dr. Nick Plant for their advice during the preparation of this manuscript. The study was supported by a Jean Shanks/Pathological Society Clinical Lecturer Grant (Grant reference: JSPS CLG 2019 02) (awarded to JM).

**Author contributions**
J.M. and M.S. designed the study. J.M. and V.B. analysed data. All authors contributed to the preparation of the manuscript.

**Competing interests**
The authors declare no competing interests.

**Additional information**
**Supplementary Information** The online version contains supplementary material available at [https://doi.org/10.1038/s41598-021-82160-0](https://doi.org/10.1038/s41598-021-82160-0).

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