Kidney and Bladder Outcomes in Children with Hemorrhagic Cystitis and BK Virus Infection after Allogeneic Hematopoietic Stem Cell Transplantation

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BK virus (BKV) infection is associated with hemorrhagic cystitis (HC) in hematopoietic stem cell transplantation (HSCT) recipients and nephropathy after kidney transplantation. We assessed the association between BKV and kidney and bladder complications in children developing HC by retrospectively reviewing 221 consecutive pediatric allogeneic HSCT recipients at the Children's Hospital of Philadelphia from 2005 to 2011. We included all patients with BKV PCR testing performed for clinical indication from day 0 until 1 year post-HSCT (N = 68). We assessed the association of any BKV infection (urine and/or blood) or peak BK viremia $\geq$ 10,000 copies/mL (high viremia) with severe HC (defined as grade IV—bladder catheterization or surgical intervention); the need for dialysis; serum creatinine—estimated glomerular filtration rate at the time of BKV testing, day 100, and day 365; and death. Children with high viremia more likely developed severe HC compared with those with peak viremia < 10,000 copies/mL (21% versus 2%; P = .02). BKV infection of the blood or urine was not associated with the need for dialysis, change in estimated glomerular filtration rate, or mortality. BKV infection is common after pediatric allogeneic HSCT, and plasma testing in those with HC may predict patients who will develop severe bladder injury.

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INTRODUCTION

BK virus (BKV) is a DNA polyoma virus that infects most of the general population, with seroprevalance rates approaching 90% by 10 years of age [1]. After primary infection, the virus remains dormant in the uroepithelial cells of the kidney and bladder [2]. Clinical disease from BKV infection is almost exclusively seen in immunocompromised patients, particularly kidney transplantation and hematopoietic stem cell transplantation (HSCT) recipients [3,4]. After HSCT, BKV infection identified in the urine (viruria) and/or blood (viremia) may be associated with hemorrhagic cystitis (HC) [5,6]. BKV viremia after renal transplantation contributes to kidney injury (nephropathy), typically in the absence of symptomatic HC, and may lead to allograft loss [2].

HC is a frequent complication of allogeneic HSCT, occurring in up to 25% of patients [4]. HC can be associated with significant morbidity and mortality, including prolonged hospitalization, invasive surgical procedures to manage bleeding, and acute kidney injury from urinary tract obstruction [7-9]. Early-onset HC is secondary to direct toxicity from the preparative conditioning regimen [3]. Late-onset HC typically occurs after the first week after transplantation and is associated with infections, such as BKV, or, less commonly, adenovirus and cytomegalovirus (CMV) [9].

Kidney and bladder injury are common complications after HSCT, and chronic kidney disease is often considered idiopathic in this population [10]. The relationship between BKV infection and kidney disease in HSCT recipients has not been well studied. Case reports suggest that BKV infection may also contribute to nephropathy in the native kidneys of HSCT and nonrenal solid-organ transplantation recipients, even in the absence of HC [11-14]. Only 2 prior studies in patients undergoing HSCT, 1 in adults [15] and the other in children [16], investigated if BKV infection identified in the blood (viremia) is a risk factor for intrinsic kidney injury. Our objective was to assess the impact of BKV infection on the severity of genitourinary outcomes in children undergoing HSCT for predominately malignant indications. We hypothesized that BK viremia would be associated with more severe kidney and bladder injury in children undergoing allogeneic HSCT.

METHODS

We reviewed the records of all children undergoing allogeneic HSCT at the Children's Hospital of Philadelphia from January 2005, when BKV PCR testing became clinically available, until March 2012. We included any patient with BKV PCR testing of blood or urine performed from day 0 until 1 year post-HSCT. We excluded patients undergoing autologous HSCT and any patient without at least 1 blood or urine BK PCR test. The protocol was approved by our center's institutional review board.

At our institution, BKV testing is performed only for a clinical indication (no routine screening) and almost exclusively in patients with concern for HC due to gross hematuria and/or urinary symptoms. Testing is typically performed first with a urine PCR. Subsequent plasma testing is also ordered at the discretion of the attending physician but usually for those patients with a positive urine PCR or persistent symptoms.

Separate BKV exposures were considered. First, patients with a positive BKV urine PCR (viruria, > 0 copies/mL) were compared with those without viruria. Additionally, subjects with plasma PCR testing were compared using the quantitative value of their peak level of viremia during the first year after transplantation. Using viral PCR thresholds reported in kidney transplantation patients with BK viremia [4] and HSCT recipients with adenoviremia [17], subjects were categorized as having a peak plasma viral load $\geq$ 10,000 copies/mL (high viremia) or <10,000 copies/mL (low viremia). Because viremia is rare in patients without viruria, patients with negative
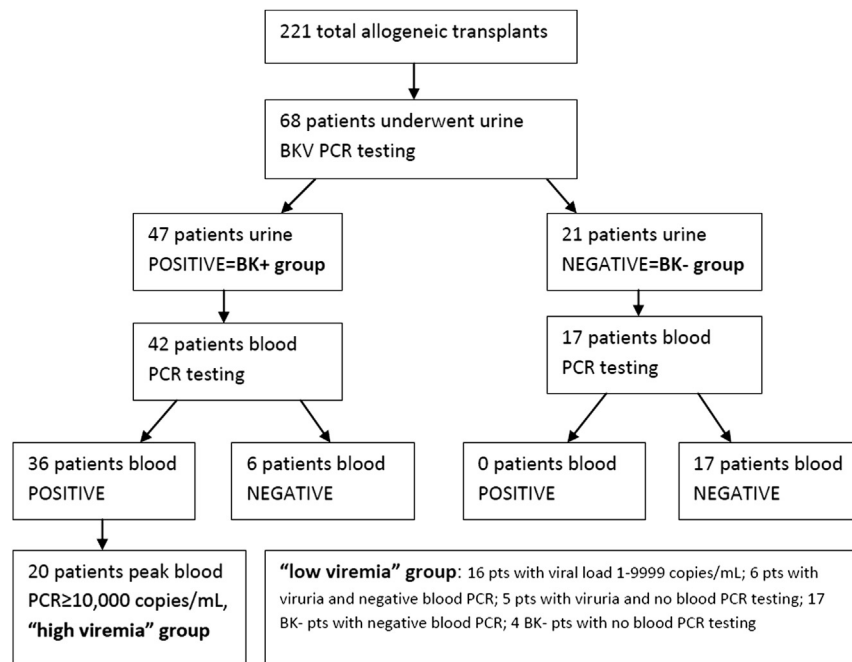
Figure 1. Flowchart depicting categorization of subjects based on BKV urine and plasma testing.

urine testing who did not have plasma testing were included in the low-viremia group.

The following separate outcomes were assessed: percent change in baseline serum creatinine-based estimated glomerular filtration rate (eGFR) at day 100, day 365, and the time of BKV infection; the need for dialysis at any point between day 0 and the end of follow-up; and the severity of HC. Overall survival and transplantation-related mortality were also considered as outcomes. Transplantation-related mortality was defined as nonrelapse death.

Each subject's mean serum creatinine level was recorded during the 14 days before the initiation of the conditioning regimen (baseline) and during the 14-day periods around day 100 and day 365. The creatinine on the first day of BKV testing was also obtained from the medical record. The eGFR was calculated with the modified Schwartz formula [18] (.413 × height [cm]/ serum creatinine [mg/dL]), using the height at time of initiation of the conditioning regimen.

Urinalyses and the clinical record from the time of BKV testing were reviewed, and the severity of HC was classified according to published criteria: grade 0, no hematuria; grade I, microscopic hematuria; grade II, gross hematuria; grade III, gross hematuria with clots; grade IV, need for catheterization or surgical intervention [19,20]. We defined "severe HC" as patients with grade IV disease.

Patients with positive CMV or adenovirus blood PCR testing (>0 copies/mL) within 2 weeks before or after BKV testing were classified as having a concomitant viral infection. At our institution, blood CMV and adenovirus PCR testing are sent for clinical indication, weekly surveillance in all recipients of allogeneic T cell–depleted or cord blood grafts, and in all patients receiving alemtuzumab. In addition, CMV screening occurs in all recipients of matched related donor transplantations if either the donor or recipient is CMV positive.

BKV testing was performed using a real-time TaqMan quantitative PCR assay with nucleic acid primer/probe pairs specific for conserved regions of the BK virus genome (Roche Molecular Systems, Pleasanton, California). In our hospital's clinical laboratory, the assay can quantitate the viral load in urine or blood above a lower threshold of 302 copies/mL. Hospital protocol is to first test for BKV using a qualitative PCR, followed by quantitative testing for initial positive results.

The dates and viral load of all BKV quantitative measurements in blood and urine were recorded from the start of conditioning until 1 year after transplantation. Baseline demographic and transplantation data were collected, including age, gender, underlying condition, conditioning regimen, stem cell source, donor type, time to neutrophil and platelet engraftment, incidence of veno-occlusive disease, incidence and grading of acute and chronic graft-versus-host disease (GVHD), and survival up to 1 year or at time of last follow-up. In addition, we reviewed documentation regarding medical and surgical management of HC and the need for dialysis.

When BKV infection was treated with cidofovir, it was administered at a low dose of .25 mg/kg every 2 weeks [21].

Because the patient population in this study was heterogeneous in terms of underlying disease, the transplantation regimen was highly variable. For patients receiving myeloablative conditioning for hematologic malignancy, the conditioning regimen consisted of either busulfan/cyclophosphamide or cyclophosphamide/total body irradiation, with or without thiotepa. A subset of patients also received horse antithymocyte globulin. Recipients of reduced-intensity conditioning regimens generally received fludarabine, melphalan, and alemtuzumab. Infectious prophylaxis varied by risk factors and graft type but in general included acyclovir for herpes simplex virus/varicella zoster virus, intravenous immune globulin for those at risk of CMV, foscarnet in patients at high risk for CMV, fluconazole, and oral gentamicin/amoxicillin for gut decontamination. All patients received a calcineurin inhibitor for GVHD chemoprophylaxis (infusional cyclosporine followed by enteral tacrolimus). Additional GVHD prophylaxis included short-course methotrexate in bone marrow recipients, corticosteroids in cord blood recipients, mycophenolate mofetil in reduced-intensity conditioning recipients, and partial ex vivo T cell depletion in growth factor–mobilized peripheral blood stem cell graft recipients.

Baseline demographic and transplantation characteristics were compared using chi-square or Fisher exact tests for categorical data, as appropriate. Continuous variables were compared using the Wilcoxon rank-sum test. Relative risks of developing the separate outcomes of severe HC or dialysis were calculated based on the presence of viruria or the degree of viremia (high viremia versus low viremia). Analysis of covariance was used to test the association between the peak quantitative urine or plasma PCR viral load and eGFR at the time of BK testing, 100 days, or 365 days, controlling for eGFR value at baseline. Quantitative viral load measurements were logarithmically transformed to account for skewed distribution. For mortality outcomes, survival analysis was performed using the Kaplan-Meier method and the log-rank test for comparisons between groups. All statistical analyses were performed using Stata 12.1 (StataCorp LP, College Station, Texas) and SAS 9.2 (SAS Institute, Cary, NC), and a 2-sided $P < .05$ was considered significant.

RESULTS

Study Population

From January 2005 to March 2012, BKV testing (urine and/or plasma) was performed in 68 of 221 patients (30.8%) undergoing allogeneic HSCT at our center (Figure 1). Testing was almost exclusively performed for symptomatic HC, with only 2 subjects having testing sent for evaluation of persistent fever, both of whom were included in the final analyses.

Table 1
Demographic and Clinical Characteristics by BK Viremia Status

	High Viremia (N = 20)	Low Viremia (N = 48)	P Value
Age, y	10.3 (5.3-17.8)	11.9 (.5-23.25)	.96
Female gender	7 (35.0)	23 (47.9)	.42
Underlying disease			
Malignant	17 (85.0)	36 (75.0)	.53
Nonmalignant	3 (15.0)	12 (25.0)	
Conditioning			
Myeloablative	18 (90.0)	42 (87.5)	1.0
Reduced intensity	2 (10.0)	6 (12.5)	
Donor type			
Matched sibling	2 (10.0)	19 (39.6)	.02
Alternative	18 (90.0)	29 (60.4)	
Stem cell source			
Bone marrow	4 (20.0)	20 (41.7)	.19
Peripheral blood	13 (65.0)	20 (41.7)	
Cord blood	3 (15.0)	8 (16.7)	

Values are medians with ranges in parentheses or n with percents in parentheses. P values calculated using Fisher exact test for categorical variables and Wilcoxon rank-sum for continuous variables.

Of the 68 patients undergoing testing for BK viruria, 47 (69.1%) were positive in the urine. The remaining 21 subjects had negative urine testing during the study period and comprised the BK-negative group.

Of the 47 viruric patients, 42 underwent plasma PCR testing for BKV, and 36 were positive. Twenty of these viremic patients had a peak plasma PCR viral load $\geq$ 10,000 copies/mL (high viremia). Of the 21 patients without viruria, 17 underwent plasma PCR testing, and none was positive. Therefore, a total of 59 patients underwent plasma testing. The low- viremia group included subjects with peak plasma viral loads <10,000 copies/mL, those without viremia, and those without plasma testing but no viruria (Figure 1).

Most study subjects underwent myeloablative conditioning (88.2%) for a malignant indication (77.9%) and received a transplant from an unrelated donor (69.1%). There were no statistically significant differences in the clinical characteristics of age, gender, underlying disease, conditioning (myeloablative versus reduced intensity), donor type, and stem cell source between patients with and without viruria. Patients with high viremia were more likely to have received grafts from alternative donors compared with those with low viremia, but otherwise demographic and transplantation characteristics were also similar between these viremia groups (Table 1).

BKV Infection Characteristics

The 47 viruric patients had a median peak urinary viral load of 2.6×10^{10} copies/mL (range, 3270 to 8.2×10^{11} copies/mL). The peak urinary viral load exceeded 1 billion copies/mL in 38 patients (80.9%). For those patients with any viremia (plasma PCR > 0 copies/mL) the median peak plasma load was 12,780 copies/mL (range, 202 to 5.5×10^7 copies/mL).

Initial BKV testing occurred at a median of day 36 (interquartile range, 8 to 83 days after HSCT) in the patients with viruria and day 24 (interquartile range, 8 to 58 days after HSCT) in the patients without viruria ($P = .15$).

The first BKV urine PCR test was sent a median of 1 day (range, 0 to 38 days) after the development of HC. A median of 1.5 urine tests (range, 1 to 8 tests) were sent per patient, and 24 viruric patients (51.1%) had more than 1 urine PCR assessment. Of those with at least 2 measurements, BK viruria was monitored over a median span of 25 days (range, 4 to 130 days). In viremic patients, the median time from development of HC to the first plasma test was 2 days (range, 0 to 76 days). Twenty-two viremic patients (61.1%) underwent repeat plasma PCR testing (median, 2; range, 1 to 9) over a median span of 23 days (range, 1 to 137 days). Forty percent of viremic patients and 43.5% of viruric patients with multiple measurements were monitored for a span of more than 30 days. There were no differences in the time to the first urine or plasma measurement, number of samples tested, or the span over which testing was performed between patients with or without viruria. Patients with high viremia had more urine (but not plasma) samples checked (median 2 versus 1; $P = .046$) over a longer time period (median 44.5 days versus 11 days; $P = .01$) than those with low viremia.

Of patients with viruria, 18 of 47 (38.3%) received cidofovir to treat BKV infection. More patients with high viremia received cidofovir (73.3%) than those that were BK positive but with low viremia (41.2%) ($P = .067$). In addition, more patients with severe HC (grade IV) received cidofovir (80%) compared with those with grades 0 to III (36%) ($P = .06$).

Severity of HC

Among the 47 patients with viruria, 39 (83.0%) had HC grade II or worse, and 5 (10.6%) had severe HC (grade IV). Two other patients had BK testing for evaluation of persistent fever, and 1 patient was tested for indeterminate reasons. Severe HC was more likely in patients with high viremia as compared with those with low viremia (21.1% versus 2.2%, respectively; $P = .023$). Although the peak plasma viral load in patients with severe HC was quantitatively and significantly higher than in patients with lower grade HC ($P = .004$), the peak urine viral load was not associated with the grade of HC ($P = .95$) (Table 2).

Kidney Injury

In all 68 patients undergoing BKV PCR testing, serum creatinine-based eGFR decreased from a median of 113.4 mL/min/1.73 m^2 at baseline to 102.7 mL/min/1.73 m^2 at day 100 ($P = .03$) and to 97.0 mL/min/1.73 m^2 at day 365 ($P < .001$). The absolute levels of eGFR and mean percent changes from baseline based on BKV status are summarized in Table 3. There were no differences in mean percent change from baseline eGFR as measured at time of BKV testing, day 100,

Table 2
Peak Plasma and Urine Viral Loads by Outcome

Viral load	HC		P Value	Dialysis		P Value	TRM		P Value
	Grades 0-III (N = 51)	Grade IV (N = 5)		No Dialysis (N = 59)	Dialysis (N = 7)		Alive at 1 y (N = 52)	Dead at 1 y (N = 16)	
Peak urine, copies/mL	1.25×10^{10}	1.96×10^{10}	.95	7.97×10^9	2.86×10^{10}	.59	5.43×10^9	1.31×10^{10}	.73
Peak plasma, copies/mL	2,378	2,460,000	<.01	2,378	26,110	.23	2476	1826.5	.79

Values are medians. P values calculated using Wilcoxon rank-sum tests to compare viral loads for each outcome. TRM indicates transplant-related mortality.

Table 3
Serum creatinine-eGFR by BK Viruria and Viremia Status

| | Viruria Status | | | | Viremia Status | | | |
| | Viruria | | No Viruria | | High Viremia | | Low Viremia | |
	eGFR	% Δ	eGFR	% Δ	eGFR	% Δ	eGFR	% Δ
Baseline	119.4	—	110.1	—	113.0	—	117.5	—
Time of BK	108.5	−6.8	105.2	−3.4	110.7	−1.8	109.7	−5.2
Day +100	103.7	−1.3	96.9	−9.4	126.7	+14.6	104.5	−10.9
Day +365	92.9	−15.7	97.6	−12.1	102.2	−6.3	97.3	−18.0

eGFR estimated with the updated Schwartz formula. eGFR values presented as median mL/min/1.73m^2. %Δ are the mean percent changes in eGFR relative to baseline (ie, a negative value indicates a decrement in eGFR).

and day 365 in those with and without viruria. Similarly, there were was no significant decrement in eGFR at the same time intervals in those with high versus low viremia. At day 100, the mean percent decrement in eGFR was significantly higher in low viremia than high-viremia patients, contrary to expectations, but this effect was abrogated by day 365.

Five patients with viruria (10.6%) and 2 patients without viruria (9.5%) required dialysis at any point post-HSCT ($P = .92$). High viremia was not associated with the need for dialysis ($P = .43$). There was a trend toward a higher peak plasma and urine viral load in patients requiring dialysis, but neither of these differences reached statistical significance (Table 2). The results were the same when subjects in whom dialysis was initiated before first BKV PCR (n = 3) were excluded from the analysis (data not shown).

Additional Transplantation Outcomes

Table 4 summarizes additional transplantation outcomes for the study population by BK viremia status. There was a trend toward more grade III to IV acute GVHD, chronic GVHD, and veno-occlusive disease in high-viremia patients compared with those with low viremia, although none of these differences reached statistical significance. Similarly, there was a nonsignificantly higher incidence of a concomitant viral infection (CMV, adenovirus, either virus, or both viruses) in high versus low- viremia patients.

Table 4
Transplantation Outcomes by BK Viremia Status

	High Viremia (N = 20)	Low Viremia (N = 48)	P Value
Engraftment, days			
ANC > 500	15 (11-19)	17 (11-27)	.12
Platelets > 20K	19 (16-33)	20 (11-44)	.69
Acute GVHD incidence			
Any	12 (66.7)	27 (62.8)	1.0
Grades II-IV	10 (50.0)	19 (39.6)	.59
Grades III-IV	7 (35.0)	10 (20.8)	.18
Chronic GVHD incidence			
Any	7 (41.2)	9 (27.3)	.35
Extensive	4 (20.0)	6 (12.5)	.47
VOD	4 (20.0)	3 (6.3)	.18
Virus			
CMV	8 (40.0)	10 (20.8)	.13
Adenovirus	5 (25.0)	6 (12.5)	.28
Either	11 (55.0)	14 (29.2)	.06
Both	2 (10.0)	2 (4.2)	.58
TRM at 1 year	25.0%	22.9%	1.0
OS at 1 year	65.0%	75.0%	.55

Values are medians with interquartile ranges in parentheses or n with percents in parentheses. *P* values calculated using Fisher exact test for categorical variables, Wilcoxon rank-sum for continuous variables, and log-rank test for survival. ANC indicates absolute neutrophil count; OS, overall survival; TRM, transplantation-related mortality; VOD, veno-occlusive disease.

Overall survival at 1 year did not differ significantly between those with or without viruria (71.1% and 65.0%, respectively) or between the high and low-viremia groups (65.0% and 75.0%, respectively). Neither urinary nor plasma peak viral load predicted the 1-year overall survival rate, and the median urine and plasma peak viral loads were similar between subjects that survived to 1 year post-HSCT and those that did not (Table 2). Similarly, there were no statistically significant differences between transplantation-related mortality based on either viruria or high viremia status (Table 4).

DISCUSSION

BKV infection is known to be associated with HC in adults and children undergoing HSCT [5,6] and may also be associated with direct kidney injury [11-16], as seen in kidney transplantation recipients [2]. We found that viremia, but not viruria, was associated with more severe bladder injury (higher grade HC) in a retrospective cohort of children after allogeneic HSCT. In contrast, neither viremia nor viruria was associated with lower serum creatinine-eGFR, the need for dialysis, or mortality. The strengths of our analysis include follow-up to 1 year; assessment of kidney, bladder, and overall outcomes; and the inclusion of a large pediatric allogeneic HSCT population. Our study was limited by the retrospective reporting of clinical data and nonsystematic measurement of BK virus infection in all subjects.

The timing and prevalence of BKV-related HC in our patients is consistent with prior reports [9,16]. The magnitude of the PCR-measured viral loads in the urine and plasma was also similar to a study in children after HSCT [16]. We found no association between acute GVHD and the timing of engraftment and BKV infection, although there was a trend toward more severe acute GVHD in patients with high viremia. Others have speculated that BKV infection in HSCT recipients is related not only to the degree of immunosuppression but also to direct tissue injury [22]. Because GVHD is associated with both augmented immunosuppression and tissue damage [23], one might expect a higher rate of GVHD in those with BKV infection. The high rate of GVHD in both viruric and nonviruric patients may explain our inability to detect an effect, possibly because most transplantations were high risk (alternative donors) compared with the general allogeneic transplantation population.

The threshold for defining "high viremia" as a PCR viral load ≥ 10,000 copies/mL was originally described in kidney transplantation recipients with biopsy-proven nephropathy [2]. In children receiving HSCT, high viremia has been associated with the need for invasive procedures for HC, increased post-HSCT creatinine, dialysis, and end-stage renal disease [16]. We also observed an association between high viremia and the severity of HC. Prior studies have documented BK

virus (particularly viremia) as a risk factor for developing HC [7-9,24,25]. To our knowledge, however, only 1 study [16] has identified BK viral load as predictive of the severity of bladder injury after HC. The present study included children undergoing transplantation primarily for a malignant indication, potentially broadening the applicability of the findings to a wider group of patients.

We were unable to detect an association between peak plasma PCR $\geq$ 10,000 copies/mL and creatinine-estimated kidney function or the need for dialysis. Subjects requiring dialysis did trend toward having a higher median peak plasma viral load, suggesting our study may have been underpowered to detect this difference. Peak urine viral loads were not associated with any outcome measure, a finding consistent with prior reports from both the adult and pediatric HSCT populations [16,25].

Only 2 studies have reported measures of kidney function in patients with BKV infection after HSCT [15,16]. Both studies found an association between BK viremia and impaired kidney function, measured either by absolute serum creatinine level [15] or by the maximum fold increase in serum creatinine relative to pretransplantation baseline [16], without calculating subjects' eGFR. In our population, neither viruria nor the degree of viremia was associated with a need for post-transplantation dialysis or a decrement in baseline eGFR, either at the time of BKV infection, day 100, or day 365.

Several factors may account for these discrepant findings. First, the prevalence of severe HC we observed is lower than that reported by others. Because severe HC is often associated with obstructive and nephrotoxic (eg, use of antivirals) kidney injury, differences in the rate and severity of HC across studies may explain the variable reporting of renal outcomes such as eGFR and the need for dialysis. Second, because kidney injury is multifactorial after HSCT, residual confounding of unmeasured exposures (including antibiotics, calcineurin inhibitors, and other infections) may also vary between different study populations. Third, by estimating kidney function at defined time periods, it is possible we missed the window of kidney injury, whereas other studies have reported the peak creatinine at any point after BKV detection compared with the pretransplantation baseline. Fourth, the differences in the study population may influence kidney outcomes and the risk for severe BKV infection; specifically, our cohort contained fewer patients who underwent transplantation for nonmalignant indications and more peripheral blood stem cell and umbilical cord grafts. Finally, the paucity of patients requiring dialysis and differences in outcome definitions (overall, transplantation-related, and BK-attributable mortality) limits our ability to make comparisons to previous studies.

The change in renal function over time observed in our study may be illustrative. Although not significant, it appeared there was only a modest decrease in eGFR at day 100 but a more pronounced decrease between day 100 and day 365. This may suggest it takes several months for patients with BKV infection to demonstrate changes in their kidney function. We were unable to directly evaluate this possibility because viral load measurements in viremic patients were made in a nonsystematic fashion, and only a portion of viremic patients had longitudinal surveillance of plasma viral loads.

Although serum creatinine is an established method of estimating kidney function, its concentration is highly dependent on muscle mass, potentially limiting its utility in children who have a high risk of deconditioning (after HSCT). Consistent with prior reports, it is possible serum creatinine overestimates GFR in this population [26]. Although this is the first study to calculate eGFR in children with BKV infection after HCT, where height is used as a proxy for muscle mass, this adjustment is not exact. Additionally, we used a single measurement of height (taken pretransplantation) to estimate GFR throughout the transplantation period, adding to the inaccuracy of GFR estimation in growing children. However, the relative paucity of vertical growth experienced during the immediate post-HSCT period likely offsets this factor. Future studies using muscle mass—independent methods to estimate kidney function may better define the degree of renal impairment after HSCT, both in those with and without BKV infection. One such method, serum cystatin C, is gaining more widespread use [26,27].

Importantly, our cohort consisted of only patients having PCR testing performed for a clinical indication, raising the possibility these were the sickest patients. Indeed, the observed incidence of acute GVHD exceeded that typically seen in our general allogeneic HSCT population. Only larger studies using prospective surveillance for BKV infection in all HSCT recipients will be able to address this limitation. In addition, as prior studies have documented peak BK viral loads in urine and plasma that preceded the development of HC [24], it is possible that we missed a period of more severe BKV infection and therefore misclassified patients by degree of viruria or viremia.

In conclusion, we observed a high prevalence of BKV-associated HC in children undergoing allogeneic HSCT. The severity of HC correlated with the degree of BKV viremia but not viruria. High viremia was more common in children receiving a transplant from an alternative donor. Consistent with kidney transplantation guidelines, BK viremia may be more specific for clinical disease in HSCT recipients, as compared with BK viruria [28]. In patients with HC or unexplained kidney injury after HSCT, we suggest initial testing of BKV with plasma and urine PCR assays to establish the diagnosis of BKV infection. Subsequently, if further monitoring is clinically indicated, testing should continue only with plasma. The development of targeted prophylaxis and/or treatment strategies may support the benefit of this monitoring approach in an effort to decrease the burden of severe HC. Although BKV infection was not associated with renal outcomes in the present study, future research is needed to address the impact of using more accurate measures of kidney function in this population at high risk of low muscle mass.

ACKNOWLEDGMENT

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