Clinical Infectious Diseases

MAJOR ARTICLE

The Natural History of BK Polyomavirus and the Host Immune Response After Stem Cell Transplantation

Benjamin L. Laskin,[1,2] Michelle R. Denburg,[1,2] Susan L. Furth,[1,2] Taylor Moatz,[1] Michelle Altrich,[3] Steve Kleiboeker,[3] Carolyn Lutzko,[4] Xiang Zhu,[4] Jason T. Blackard,[5] Sonata Jodele,[6] Adam Lane,[6] Gregory Wallace,[6] Christopher E. Dandoy,[6] Kelly Lake,[6] Alexandra Duell,[6] Bridget Litts,[6] Alix E. Seif,[2,7] Timothy Olson,[2,7] Nancy Bunin,[2,7] and Stella M. Davies[6]

[1]Division of Nephrology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA, [2]Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA, [3]Viracor-Eurofins, Lee's Summit, Missouri, USA, [4]Experimental Hematology and Cancer Biology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA, [5]Division of Digestive Diseases, University of Cincinnati College of Medicine, Cincinnati, Ohio, USA, [6]Division of Bone Marrow Transplantation and Immune Deficiency, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA, and [7]Division of Oncology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA

Background. BK polyomavirus (BKPyV) is associated with symptomatic hemorrhagic cystitis after hematopoietic cell transplantation (HCT). Little is known about the host immune response, effectiveness of antiviral treatment, or impact of asymptomatic replication on long-term kidney function.

Methods. In children and young adults undergoing allogeneic HCT, we quantified BKPyV viruria and viremia (pre-HCT and at Months 1–4, 8, 12, and 24 post-HCT) and tested associations of peak viremia ≥10 000 or viruria $\geq 10^9$ copies/mL with estimated kidney function (glomerular filtration rate, eGFR) and overall survival at 2 years posttransplant. We examined the factors associated with viral clearance by Month 4, including BKPyV-specific T cells by enzyme-linked immune absorbent spot at Month 3 and cidofovir use.

Results. We prospectively enrolled 193 participants (median age 10 years) and found that 18% had viremia ≥10 000 copies/mL and 45% had viruria $\geq 10^9$ copies/mL in the first 3 months post-HCT. Among the 147 participants without cystitis (asymptomatic), 58 (40%) had any viremia. In the entire cohort and asymptomatic subset, having viremia ≥10 000 copies/mL was associated with a lower creatinine/cystatin C eGFR at 2 years post-HCT. Viremia ≥10 000 copies/mL was associated with a higher risk of death (adjusted hazard ratio, 2.2; 95% confidence interval, 1.1–4.2). Clearing viremia was associated with detectable BKPyV-specific T cells and having viremia <10 000 copies/mL, but not cidofovir exposure.

Conclusions. Screening for BKPyV viremia after HCT identifies asymptomatic patients at risk for kidney disease and reduced survival. These data suggest potential changes to clinical practice, including prospective monitoring for BKPyV viremia to test virus-specific T cells to prevent or treat BKPyV replication.

Keywords. BK polyomavirus; stem cell transplantation; pediatrics; kidney.

BK polyomavirus (BKPyV) is associated with nephropathy after kidney transplantation and hemorrhagic cystitis after hematopoietic cell transplantation (HCT) [1, 2]. Hemorrhagic cystitis occurs in up to 25% of patients, leading to pain, urinary obstruction, prolonged hospitalizations, and possibly increased mortality [3–5]. In immunosuppressed patients, BKPyV replication is detected by nucleic acid testing of blood (viremia) or urine (viruria). Asymptomatic viruria is common after HCT and solid organ transplant, while viremia, especially high-level replication ≥10 000 copies/mL, is more specific for kidney and bladder disease [1, 4, 6].

Single-center studies have reported viremia or viruria incidences in the first 100 days after HCT [3, 7, 8] but not the longer-term risk of asymptomatic BKPyV replication on kidney function or the host immune response. We defined the natural history of BKPyV replication and outcomes for 2 years after HCT among patients at 2 large children's hospitals and examined antiviral immunity. We hypothesized that BKPyV was associated with decreased kidney function and that the measurement of BKPyV T cells would predict viral clearance. Consensus guidelines do not recommend screening for BKPyV after HCT [5, 9] perhaps missing a risk factor for reduced kidney function or cystitis. Moreover, antivirals do not have proven efficacy, but third-party BKPyV T cells can be infused to promote viral clearance and more data are needed to define appropriate therapeutic use.

METHODS

Patient Population

We prospectively enrolled children and young adults ≥2 years of age who were undergoing an allogeneic HCT at the Children's Hospital of Philadelphia (CHOP) or Cincinnati Children's Hospital Medical Center (CCHMC) from April 2013–May 2018, with follow-up until October 2018. The Institutional

Received 17 July 2019; editorial decision 1 December 2019; accepted 16 December 2019; published online December 18, 2019.

Correspondence: B. L. Laskin, Division of Nephrology, The Children's Hospital of Philadelphia, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104 (laskinb@email.chop.edu).

Clinical Infectious Diseases® 2020;71(12):3044–54

DOI: 10.1093/cid/ciz1194

Review Boards at CHOP and CCHMC approved the study and participants provided informed consent and assent.

Laboratory Methods

Plasma, serum, peripheral blood mononuclear cells (PBMCs), and urine were frozen prior to HCT and at Months 1–4, 8, 12, and 24 (the research methods are available in the Supplementary Material). Nucleic acid testing for BKPyV was performed on all plasma and urine samples (Viracor-Eurofins, Lee's Summit, MO). Blood BKPyV immunoglobulin G (IgG) was measured at baseline and Months 3 and 12 (Viracor-Eurofins). Enzyme-linked immunosorbent spot (ELISPOT) testing to detect BKPyV-specific T cells was performed on Month 3 PBMC samples (Figure 1).

Clinical Data

Clinical data were abstracted from the medical record, including serum creatinine and absolute lymphocyte counts within ±1 day of when 1049 of the 1070 (98.0%) research blood samples were collected (Supplementary Table 1). We recorded participants receiving cidofovir for any indication. Epstein-Barr virus, cytomegalovirus, adenovirus, and human herpes virus 6 viremia were captured from center-specific monitoring; positivity was defined using ≥2 consecutive nucleic acid results at any time posttransplant. Blood cystatin C was measured clinically or on stored samples at baseline and at Months 8, 12, and 24 [10].

BK Polyomavirus Definitions, Outcome Variables, and Covariates

BKPyV replication was defined as a positive nucleic acid test, with or without clinical symptoms, and was categorized as peak viremia ≥10 000 copies/mL [1, 4, 6] and/or viruria ≥10^9 copies/mL [11, 12] among participants with ≥2 samples during the first 3 months post-HCT. The outcomes included cystitis, estimated glomerular filtration rate (eGFR), dialysis, and all-cause death. Cystitis was defined as grade ≥2 (presence of BKPyV, symptoms, and visible hematuria [2, 5]) and was assessed retrospectively by reviewing clinical documentation. GFR was estimated at baseline and at Months 8, 12, and 24. For participants <18 years of age [13] and ≥18 years of age [14], eGFRs were separately calculated using serum creatinine alone and cystatin C and creatinine together. We analyzed eGFR in the whole cohort and in the subset with asymptomatic viral replication (no cystitis). Covariates included demographic and transplant characteristics, graft-versus-host disease (GVHD), thrombotic microangiopathy (TMA), cidofovir for any indication, and other viremias. TMA was only assessed at CCHMC due to an established screening guideline [15]. As a risk factor for BKPyV replication, other viremias, GVHD, and TMA were not analyzed as time-dependent variables and could have occurred before or after detectable BKPyV. As a risk factor for cystitis, acute GVHD was only considered if it occurred prior to cystitis.

Immune Response and Viral Clearance

We examined whether the baseline IgG predicted posttransplant replication. We tested the Month 3 PBMC sample for BKPyV-specific T cells, defined as those with ELISPOT counts >5 or >10 above the negative control. We hypothesized that among participants with persistent BKPyV replication (≥2 positive samples) in the first 3 months posttransplant, a positive ELISPOT would predict viral clearance (undetectable viral DNA) at Month 4. We also assessed other factors potentially associated with clearance, including the absolute lymphocyte count, IgG, and cidofovir use.

Statistical Analyses

Continuous variables were presented as medians and interquartile ranges (IQR) and were examined with the Wilcoxon rank sum or 2-sample *t* test, as appropriate. Categorical variables were examined with the Chi-square or Fisher's exact test, as appropriate. Logistic regression examined the factors associated with viral clearance. We excluded those participants developing cystitis prior to their Month 1 sample, to examine whether BKPyV replication predicted later cystitis. Linear regression examined the factors associated with eGFR. Multivariable Cox proportional hazards regression assessed the associations among BKPyV, cystitis, and mortality. Model selection for cystitis was performed with backward elimination using likelihood ratio testing and for mortality included all significant plausible variables. Given the high mortality rate, we also examined cystitis in a competing risk regression with death. We examined the overall survival rate instead of the nonrelapse mortality rate, given the high proportion of nonmalignant transplant indications. The study was originally designed to have 85% power to detect a clinically meaningful difference in a 1-year eGFR of 20 ml/min/1.73m^2 between participants with and without BKPyV viremia ≥10 000 copies/mL and assumed a sample size of 100 participants surviving to 1 year and a 10% prevalence of viremia. Analyses were performed using STATA Version 15.1 and R 3.5.1, and a 2-sided *P* value <.05 was considered statistically significant.

RESULTS

Cohort

We enrolled 193 participants (Figure 1; Table 1), who had a median age of 10 years (IQR, 6–15 years; range, 2–32 years). The most common underlying diagnoses were malignancy (37%), bone marrow failure (27%), or immunodeficiency (21%). At CCHMC (n = 148), a greater proportion of participants had bone marrow failure or immunodeficiency, compared to CHOP (n = 45), where most participants had malignancy. The cohort characteristics by center, specific underlying diagnoses, and conditioning regimens are shown in Supplementary Tables 2–4.

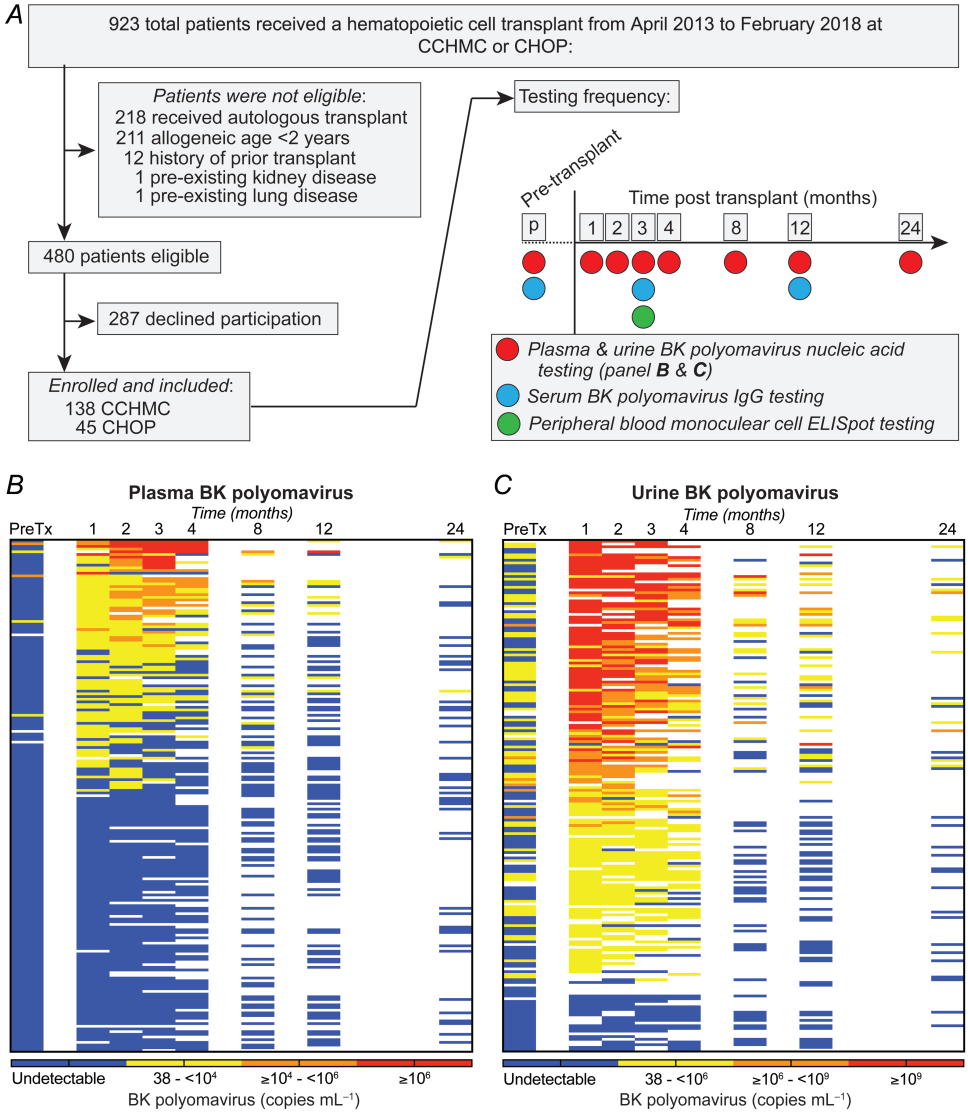

Figure 1. Study cohort, sampling, and testing frequency and BK polyomavirus (BKPyV) viremia and viruria after hematopoietic cell transplant. *A*, We tested 193 children and young adults for BK polyomavirus in the blood (viremia) and urine (viruria) in the first 2 years after hematopoietic cell transplant (exclusion criteria in Supplementary Methods). Samples were collected and analyzed prior to transplant and at Months 1, 2, 3, 4, 8, 12, and 24 after transplant. *B*, Viremia was rare prior to transplant, occurred most frequently in the first 4 months, and, among survivors, was less frequent >8 months after transplant. *C*, Viruria was common prior to transplant, occurred frequently in the first 4 months, and persisted among a high proportion of survivors >8 months after transplant. Note that the scales are different for viremia and viruria. Abbreviations: CCHMC, Cincinnati Children's Hospital Medical Center; CHOP, Children's Hospital of Philadelphia; ELISPOT, enzyme-linked immune absorbent spot; IgG, immunoglobin G; PreTX, pretransplant.

BK Polyomavirus Replication

BKPyV results are shown in Figure 1 and Tables 2 and 3. We tested 1070 blood samples (median, 6 samples/participant; IQR, 5–7 samples). Only 5 of 188 (2.7%) participants had viremia pre-HCT. Of 190 participants, 94 (49.5%) had ≥1 sample with detectable viremia after transplant. Among participants with ≥2 samples in the first 3 months after transplant and with negative pre-HCT viremia, the viral load was ≥10 000 copies/mL in 32 of 178 (18.0%). In univariate analyses, the risk factors significantly associated with viremia ≥10 000 copies/mL included an older recipient age, unrelated donor, older donor age, antithymocyte globulin or cyclophosphamide conditioning (but not alemtuzumab), detectable pre-HCT viruria, and a lower Month 2 absolute lymphocyte count (Table 1). Viremia ≥10 000 copies/mL was associated with acute GVHD grade ≥2 (odds ratio [OR], 2.5; 95% confidence interval [CI], 1.2–5.4; $P = .02$) at any time relative to transplant (not time-dependent). Among the CCHMC participants, viremia ≥10 000 copies/mL was associated with TMA (OR, 7.0; 95% CI, 2.4–20.0; $P < .001$) at any time relative to transplant (not time-dependent). At Months 8, 12, and 24, 12 of 85 (14.1%), 9 of 91 (9.9%), and 3 of 44 (6.8%) participants had detectable viremia, respectively.

We tested 890 urine samples (median, 5 samples/participant; IQR, 3–6 samples). Pre-HCT, one-third of participants

Table 1. Cohort Characteristics and Variables Associated with Peak BK Polyomavirus Viremia ≥10 000 Copies/mL in the First 3 Months After Hematopoietic Cell Transplant

Variable	Entire Cohort N = 193	<10 000 Copies/mL N = 178[b] n = 146	≥10 000 Copies/mL N = 178[b] n = 32	*P*[a]
Age at transplant, years	10 (6–15)	10 (6–14)	12 (9–17)	.02
Recipient male gender	112 (58.0%)	82 (56.2%)	21 (65.6%)	.33
Diagnosis group				.63
Malignancy	72 (37.3%)	52 (35.6%)	12 (37.5%)	
Bone marrow failure	52 (26.9%)	38 (26.0%)	11 (34.4%)	
Immunodeficiency	40 (20.7%)	30 (20.5%)	6 (18.8%)	
Other	29 (15.0%)	26 (17.8%)	3 (9.4%)	
Unrelated donor, versus related	130 (67.4%)	94 (64.4%)	28 (87.5%)	.01
Donor age, years	24 (16–31)	24 (15–29)	28 (23–36)	.01
Donor/recipient gender mismatch	86 (44.6%)	68 (46.6%)	15 (46.9%)	.98
10/10 HLA match, versus another match	143 (74.1%)	115 (78.8%)	20 (62.5%)	.05
Donor HLA C7 allele	107 (55.4%)	80 (54.8%)	15 (46.9%)	.42
Cell product			-	.45
Bone marrow	123 (63.7%)	96 (65.8%)	18 (56.3%)	
Peripheral blood stem cells	64 (33.2%)	45 (30.8%)	14 (43.8%)	
Cord blood[c]	6 (3.1%)	5 (3.4%)	0 (0%)	
Conditioning chemotherapy				
Received alemtuzumab	51 (26.4%)	40 (27.4%)	6 (18.8%)	.31
Received antithymocyte globulin	80 (41.5%)	54 (37.0%)	20 (62.5%)	.01
Received cyclophosphamide	109 (56.5%)	76 (52.1%)	23 (71.9%)	.04
Received busulfan	84 (43.5%)	65 (44.5%)	14 (43.8%)	.94
Received total body irradiation	45 (23.3%)	30 (20.5%)	9 (28.1%)	.35
Myeloablative conditioning	129 (66.8%)	95 (65.1%)	23 (71.9%)	.46
Graft-versus-host disease prophylaxis				
Received calcineurin inhibitor	157 (81.4%)	118 (80.8%)	26 (81.3%)	.96
Received ex vivo T-cell depletion	55 (28.5%)	40 (27.4%)	12 (37.5%)	.26
Epstein-Barr virus viremia[d]	85 (44.0%)	65 (44.5%)	15 (46.9%)	.81
Cytomegalovirus viremia[d]	60 (31.1%)	49 (33.6%)	9 (28.1%)	.55
Adenovirus viremia[d]	33 (17.1%)	21 (14.4%)	5 (15.6%)	.79
Human herpes virus 6 viremia[d]	12 (6.2%)	8 (5.5%)	1 (3.1%)	1.00
Detectable pretransplant viruria	69 (39.7%)	46 (34.3%)	19 (63.3%)	.003
Month 1 absolute lymphocyte count	410 (190–720)	460 (220–790)	383 (195–595)	.35
Month 2 absolute lymphocyte count	530 (280–900)	610 (300–1090)	375 (150–620)	.01
Month 3 absolute lymphocyte count	726 (400–1140)	740 (430–1270)	695 (260–980)	.15

Data are shown as either a median (interquartile range) or n (%).

Abbreviation: HLA, human leukocyte antigen.

[a]*P* value by Wilcoxon rank sum, 2-sample *t* test, Chi-square, or Fisher's exact test, as appropriate, comparing viremia with <10 000 copies/mL to those with ≥10 000 copies/mL.

[b]Includes 178 participants with ≥2 blood tests (n = 10 with <2 blood tests) in the first 3 months and negative pretransplant viremia (n = 5 with detectable pretransplant viremia).

[c]Of 6 cord blood transplant recipients, 5 also received bone marrow–derived cells.

[d]Occurring at any point posttransplant.

(69 of 174, 39.7%) had detectable viruria, with a median of 3500 copies/mL (IQR, 1000–4 242 400 copies/mL). Of 184 participants, 160 (87.0%) had ≥1 sample with viruria after transplant. The peak urine viral load was $\geq 10^9$ copies/mL in 70 of 157 (44.6%) participants with ≥2 urine samples in the first 3 months posttransplant. Approximately half of participants with viruria also experienced viremia (90 of 160, 56.3%). Viremic participants essentially all also had viruria, with only 1 participant with viremia (a single value of 112 copies/mL) having no viruria.

Clinical Outcomes

Hemorrhagic Cystitis

BKPyV-associated cystitis was identified in 43 of 193 (22.3%) participants at a median of 34 days (IQR, 25–54 days) post-HCT. Any detectable viremia or viruria $\geq 10^9$ copies/mL significantly predicted subsequent cystitis (Table 4). Of note, exposure to busulfan was also associated with an increased risk of cystitis (39.3% with no exposure versus 58.1% with exposure; $P = .03$), but cyclophosphamide was not (54.0% versus 65.1%; $P = .2$). In a multivariable model adjusting for significant covariates

Table 2. BK Polyomavirus Viremia Sample Results by Time Point

Copies/mL	Pre-HCT n = 188	Month 1 n = 185	Month 2 n = 178	Month 3 n = 165	Month 4 n = 134	Month 8 n = 85	Month 12 n = 91	Month 24 n = 44
0	183 (97.3%)	112 (60.5%)	105 (59.0%)	110 (66.7%)	101 (75.4%)	73 (85.9%)	82 (90.1%)	41 (93.2%)
1–9999	3 (1.6%)	67 (36.2%)	52 (29.2%)	30 (18.2%)	20 (14.9%)	10 (11.8%)	8 (8.8%)	3 (6.8%)
10 000–99 999	2 (1.1%)	3 (1.6%)	16 (9.0%)	15 (9.1%)	8 (6.0%)	2 (2.4%)	0 (0%)	0 (0%)
≥100 000	0 (0%)	3 (1.6%)	5 (2.8%)	10 (6.1%)	5 (3.7%)	0 (0%)	1 (1.1%)	0 (0%)

There were 191 participants with at least 1 blood sample tested for viremia: n represents the number of participants tested at each time point.
Abbreviation: HCT, hematopoietic cell transplant.

(Table 4), detectable viremia was independently associated with cystitis (adjusted hazard ratio [HR], 7.8; 95% CI, 3.1–19.3; $P < .01$). The model results were similar when including viruria $\geq 10^9$ copies/mL instead of viremia (adjusted HR, 5.7; 95% CI, 2.4–13.4; $P < .01$). In a competing risk regression with death, adjusted for the same covariates as shown in the final Cox models in Table 4, detectable viremia and viruria $\geq 10^9$ copies/mL remained independently associated with cystitis (adjusted HRs 7.9 [95% CI 3.1–20.4; $P < .01$] and 5.7 [95% CI, 2.4–13.2; $P < .01$], respectively.)

Kidney Outcomes

Participants with viremia ≥10 000 copies/mL in the first 3 months after transplant had a significantly lower eGFR at 12 and 24 months (Table 5) and a higher risk of receiving dialysis (OR, 6.2; 95% CI, 1.8–21.6; $P = .004$). Age, total body irradiation, cyclophosphamide, calcineurin inhibitor prophylaxis, GVHD, cystitis, and cidofovir were not associated with the Month 24 eGFR (Supplementary Table 5). Adjusting for only the baseline eGFR, participants with viremia ≥10 000 copies/mL had a Month 24 creatinine/cystatin C eGFR that was 20.2 ml/min/1.73m^2 lower (95% CI, −38.9 to −1.6 ml/min/1.73m^2; $P = .03$), compared to those with viremia <10 000 copies/mL. Viruria $\geq 10^9$ copies/mL was not associated with Month 8, 12, or 24 eGFR or dialysis (Table 5).

Among those not developing cystitis, 58 of 147 (39.5%) had viremia, including 19 of 58 (32.8%) with viremia ≥10 000 copies/mL. When limiting the data to these participants with asymptomatic viremia, both the creatinine (median, 83 versus 125 ml/min/1.73m^2, respectively; $P = .01$) and creatinine/cystatin C (median, 78 versus 117 ml/min/1.73m^2, respectively; $P = .004$) eGFRs were significantly lower at 24 months among those with viremia ≥10 000 copies/mL (n = 4), compared to those without (n = 32). Adjusting only for the baseline eGFR, participants with asymptomatic viremia ≥10 000 copies/mL in the first 3 months after transplant had a creatinine/cystatin C eGFR that was 29.4 ml/min/1.73m^2 lower (95% CI, −55.3 to −3.6 ml/min/1.73m^2, respectively; $P = .03$) than those with viremia <10 000 copies/mL (Supplementary Table 5).

Mortality

After a median follow-up of 2.2 years (IQR, .8–3.8 years), 49 of 193 (25.4%) participants died. Participants with viremia ≥10 000 copies/mL in the first 3 months after transplant had a 3-fold increased risk of all-cause mortality (HR, 2.8; 95% CI, 1.5–5.2; $P = .002$). The HR for death associated with grade ≥2 cystitis was 2.0 (95% CI, 1.1–3.6; $P = .02$). Adjusting for cystitis and other factors associated with mortality, including age, gender, underlying diagnosis, and acute GVHD grade ≥2, viremia ≥10 000 copies/mL was independently associated with mortality (HR, 2.2; 95% CI, 1.1–4.2; $P = .02$).

Immune Response and Clearance of Viremia

The distribution of BKPyV IgG is shown in Figure 2. The baseline IgG was not associated with post-HCT viruria or viremia, as participants with both the highest and lowest levels developed viremia after transplant (data not shown). The Month 3 IgG was not associated with viral clearance (Table 6 and below).

Month 3 PBMC samples were tested for BKPyV-specific T cells in 104 of 193 (53.9%) participants. We examined factors associated with viral clearance by Month 4 among the subset of 52 participants with persistent viremia in the first 3 months after transplant and with an available Month 4 sample to assess clearance (Tables 6 and 7). Clearance of

Table 3. BK Polyomavirus Viruria Sample Results by Time Point

Copies/mL	Pre-HCT n = 174	Month 1 n = 162	Month 2 n = 146	Month 3 n = 128	Month 4 n = 99	Month 8 n = 63	Month 12 n = 81	Month 24 n = 37
0	105 (60.3%)	17 (10.5%)	23 (15.8%)	20 (15.6%)	26 (26.3%)	43 (68.3%)	52 (64.2%)	24 (64.9%)
1–999 999 999	63 (36.2%)	65 (40.1%)	51 (34.9%)	53 (41.4%)	37 (37.4%)	15 (23.8%)	21 (25.9%)	11 (29.7%)
$\geq 10^6$–10^9	6 (3.5%)	21 (13.0%)	32 (21.9%)	27 (21.1%)	24 (24.2%)	3 (4.8%)	6 (7.4%)	2 (5.4%)
$\geq 10^9$	0 (0%)	59 (36.4%)	40 (27.4%)	28 (21.9%)	12 (12.1%)	2 (3.2%)	2 (2.5%)	0 (0%)

There were 189 participants with at least 1 urine sample tested for viruria: n represents the number of participants tested at each time point.
Abbreviation: HCT, hematopoietic cell transplant.

Table 4. Variables Associated With Grade ≥ 2 Hemorrhagic Cystitis After Hematopoietic Cell Transplant

	No Grade ≥ 2 Cystitis n = 150	Grade ≥ 2 Cystitis n = 43	Univariate *P*	Multivariable Cox Models, Data Shown as Hazard Ratios for Cystitis (95% CI)			
				Detectable BKPyV Viremia Pre-cystitis		BKPyV Viruria >10^9 Copies/mL Pre-cystitis	
				Full Model	Final Model	Full Model	Final Model
Age at transplant, years	10 (6–14)	11 (8–17)	.04	1.0 (.9–1.1)	…	1.0 (.9–1.1)	…
Male gender	85 (56.7%)	27 (62.8%)	.47	…	…	…	…
Diagnosis group			.83	…	…	…	…
Malignancy	54 (36.0%)	18 (41.9%)		…	…	…	…
Bone marrow failure	40 (26.7%)	12 (27.9%)		…	…	…	…
Immunodeficiency	33 (22.0%)	7 (16.3%)		…	…	…	…
Other	23 (15.3%)	6 (14.0%)		…	…	…	…
Unrelated donor, versus related	98 (65.3%)	32 (74.4%)	.26	…	…	…	…
10/10 HLA match, versus another match	117 (78.0%)	26 (60.5%)	.02	.6 (.3–1.3)	…	.7 (.3–1.7)	…
Peripheral blood stem cell product, versus bone marrow/cord	43 (28.7%)	21 (48.8%)	.01	.5 (.05–5.1)	…	.4 (.1–3.0)	…
Conditioning chemotherapy							
Received alemtuzumab	48 (32.0%)	3 (7.0%)	<.001	.1 (0–.9)[a]	.1 (.01–.7)[a]	[b]	[b]
Received antithymocyte globulin	56 (37.3%)	24 (55.8%)	.03	1.0 (.4–2.6)	…	1.7 (.7–4.2)	…
Received cyclophosphamide	81 (54.0%)	28 (65.1%)	.20	…	…	…	…
Received busulfan	59 (39.3%)	25 (58.1%)	.03	2.7 (1.0–7.6)	3.0 (1.3–6.7)[c]	1.9 (.7–4.9)	…
Total body irradiation	35 (23.3%)	10 (23.3%)	.99	…	…	…	…
Myeloablative conditioning	92 (61.3%)	37 (86.0%)	.002	.7 (.2–3.0)	…	5.5 (1.1–27.4)[a]	11.1 (2.6–48.0)[c]
Graft-versus-host disease prophylaxis							
Received calcineurin inhibitor	123 (82.0%)	34 (79.1%)	.66	…	…	…	…
Received ex vivo T-cell depletion	36 (24.0%)	19 (44.2%)	.01	2.2 (.2–23.8)	…	2.6 (.4–18.4)	…
Detectable pre-HCT BKPyV viruria	51/135 (37.8%)	18/39 (46.2%)	.35	…	…	…	…
Detectable pre-HCT BKPyV viremia	3/146 (2.1%)	2/42(4.8%)	.31	…	…	…	…
Epstein-Barr virus viremia[d]	71 (47.3%)	14 (32.6%)	.09	…	…	…	…
Cytomegalovirus viremia[d]	41 (27.3%)	19 (44.2%)	.04	3.4 (1.5–7.9)[c]	3.4 (1.6–7.4)[c]	3.2 (1.4–7.3)[c]	2.9 (1.3–6.5)[c]
Adenovirus viremia[d]	28 (18.7%)	5 (11.6%)	.36	…	…	…	…
HHV6 viremia[d]	9 (6.0%)	3 (7.0%)	.73	…	…	…	…
Acute graft-versus-host disease pre-cystitis[e]	50 (33.3%)	15 (34.9%)	.85	…	…	…	…
BKPyV viruria >10^9 copies/mL pre-cystitis[e]	48/141 (34.0%)	17/25 (68.0%)	.001	…	…	6.4 (2.5–15.9)[c]	5.7 (2.4–13.4)[c]

Table 4. Continued

	No Grade ≥ 2 Cystitis n = 150	Grade ≥ 2 Cystitis n = 43	Univariate *P*	Multivariable Cox Models, Data Shown as Hazard Ratios for Cystitis (95% CI)			
				Detectable BKPyV Viremia Pre-cystitis		BKPyV Viruria >10^9 Copies/mL Pre-cystitis	
				Full Model	Final Model	Full Model	Final Model
Detectable BKPyV viremia pre-cystitis[e]	58/147 (39.5%)	21/28 (75.0%)	<.001	7.4 (2.9–19.3)[c]	7.8 (3.1–19.3)[c]	…	…
BKPyV viremia >10 000 copies/mL pre-cystitis[e]	19/147 (12.9%)	2/28 (7.1%)	.53	…	…	…	…

Total N = 193. Univariate data are shown as a median (interquartile range) or n (%) with a univariate *P* value by Wilcoxon rank sum, 2-sample *t* test, Chi-square, or Fisher's exact test, as appropriate.

Abbreviations: BKPyV, BK polyomavirus; CI, confidence interval; HCT, hematopoietic cell transplant; HHV6, human herpes virus 7; HLA, human leukocyte antigen.

[a]*P* < .05.

[b]Not receiving alemtuzumab conditioning predicted failure perfectly and therefore was not included in the Cox models.

[c]*P* < .01.

[d]Occurring at any point posttransplant.

[e]We excluded participants without an available posttransplant research sample before the diagnosis of cystitis so that the variable had to precede the diagnosis of cystitis or occur at any time after transplant among those without cystitis.

Table 5. Kidney Outcomes Associated With BK Polyomavirus Viremia and Viruria After Hematopoietic Cell Transplant

	Peak Viremia in First 3 Months After Transplant				Peak Viruria in First 3 Months After Transplant			
		<10 000 Copies/mL	≥10 000 Copies/mL			<10^9 Copies/mL	≥10^9 Copies/mL	
	n	n = 149[b]	n = 34[b]	*P*[a]	n	n = 87[c]	n = 70[c]	*P*[a]
Baseline								
Creatinine	183	131 (112–153)	132 (108–152)	.41	157	130 (108–155)	131 (113–145)	.77
Creatinine/cystatin	183	125 (110–141)	118 (108–143)	.48	156	120 (109–141)	123 (112–140)	.42
Month 8								
Creatinine	82	121 (104–138)	98 (84–116)	.10	74	125 (98–147)	116 (100–132)	.35
Creatinine/cystatin	82	106 (92–120)	92 (82–111)	.47	74	106 (90–121)	104 (92–119)	.53
Month 12								
Creatinine	89	126 (104–148)	110 (78–125)	.02	77	119 (97–150)	124 (104–134)	.70
Creatinine/cystatin	88	110 (97–131)	100 (88–107)	.04	76	104 (94–129)	104 (91–126)	.74
Month 24								
Creatinine	43	125 (110–141)	98 (75–111)	.005	35	125 (108–137)	112 (105–131)	.34
Creatinine/cystatin	43	113 (100–127)	97 (73–104)	.003	35	115 (103–127)	106 (95–118)	.39
Received dialysis	…	5 (3.4%)	6 (17.7%)	.006	…	3 (3.5%)	6 (8.6%)	.19
Alive at last follow-up	…	122 (81.9%)	19 (55.9%)	.001	…	70 (80.5%)	50 (71.4%)	.19

Data are shown as a median (interquartile range) or n (%). Data are for the unadjusted, estimated glomerular filtration rate (mL/min/1.73m^2)

[a]*P* value by Wilcoxon rank sum, 2-sample *t* test, Chi-square, or Fisher's exact test, as appropriate.

[b]Includes the 183 participants with at least 2 samples in the first 3 months after transplant.

[c]Includes the 157 participants with at least 2 urine samples in the first 3 months after transplant.

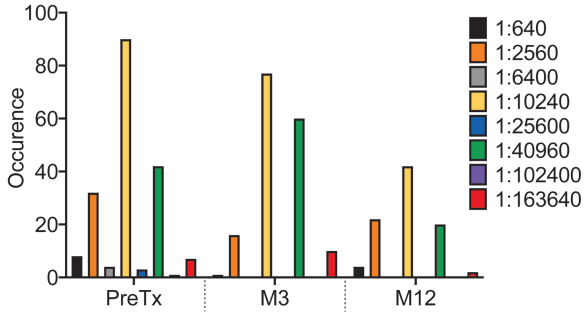

Figure 2. Distribution of BK polyomavirus immunoglobulin G titers after transplant. There were 8 participants that inadvertently had 2 separate samples run pretransplant with results that differed by one 4-fold dilution, and their titers were averaged. Abbreviations: M, month; PreTX, pretransplant.

viremia at Month 4 occurred in 21 of these 52 (40.4%) and was less likely among participants with prior viremia ≥10 000 copies/mL. The Month 3 absolute lymphocyte count did not predict clearance. Receiving cidofovir for any indication (cystitis or adenoviremia) was less likely among participants with a 10/10 matched donor and more common among those developing acute GVHD, BKPyV viremia >10 000, and viruria $\geq 10^9$ copies/mL (Supplementary Table 6). Participants with BKPyV replication who had received cidofovir were significantly less likely to clear viremia, but those with an ELISPOT >10 spots above the control were more likely to clear viremia (OR, 5.0; 95% CI, 1.3–18.6; $P = .02$; Table 6). Finally, 6 of 7 participants with persistent viremia at both Months 8 and 12 did not have detectable BKPyV-specific T cells at Month 3 (Supplementary Table 7).

DISCUSSION

We report the natural history of BKPyV replication in almost 200 children and young adults undergoing HCT at 2 large centers. A number of novel findings have the potential to change practice. First, we identified frequent asymptomatic viremia and found that high levels of viremia, whether symptomatic or not, were associated with significant reductions in later kidney function. Second, we found that children and young adults with BKPyV replication who received cidofovir were not more likely to clear viremia. Last, we identified BKPyV-specific T cells as a marker of clearing viremia but no benefit from antibody responses. The management of BKPyV at most centers currently includes testing for viral reactivation only in symptomatic cases, with the provision of additional intravenous immunoglobulin and cidofovir. While our data suggest that none of these approaches may be beneficial, randomized trials would be needed to validate the effectiveness of treatments. The screening of asymptomatic patients for BKPyV will only be beneficial if a therapy is available. Our data show that the recovery of endogenous BKPyV-specific T cells is associated with viral clearance, similar to prior studies after kidney transplantation [16–19]. To our knowledge, our study is the largest systematic evaluation of cellular responses to BKPyV after HCT [20–22]. The efficacy and safety of third-party BKPyV-specific T cells has recently been reported after HCT [23–25].

Our findings expand on single-center studies examining BKPyV in the first 100 days after HCT, which are generally without a comprehensive assessment of kidney outcomes or immune responses [11, 12, 26, 27]. Hill et al [7, 8] measured the impact of viremia from 5 viruses, including BKPyV, on

Table 6. Factors Associated With Clearance of BK Polyomavirus Viremia at 4 Months After Hematopoietic Cell Transplant

	Did Not Clear Viremia at Month 4	Cleared Viremia at Month 4	
	n = 31[b]	n = 21[b]	*P*[a]
Peak viremia ≥10 000 copies/mL in the first 3 months after transplant	21 (67.7%)	3 (14.3%)	<.001
Month 3 BK polyomavirus IgG	n = 31	n = 20	.49
1:2560	2 (6.5%)	2 (10.0%)	
1:10 240	17 (54.8%)	7 (35.0%)	
1:40 960	10 (32.3%)	8 (40.0%)	
1:163 840	2 (6.5%)	3 (15.0%)	
Month 3 absolute lymphocyte count, cells/μL	646 (260–880)	780 (500–970)	.15
Received cidofovir in first 3 months after transplant	17 (54.8%)	3 (14.3%)	.004
Month 3 ELISPOT spots above negative control	n = 25	n = 18	
Number of spots	1.3 (0–8.4)	20.1 (2.9–48.5)	.007
>5 spots	9 (36.0%)	12 (66.7%)	.05
>10 spots	6 (24.0%)	11 (61.1%)	.01

Data are shown as a median (interquartile range) or n (%).

Abbreviation: ELISPOT, enzyme-linked immune absorbent spot.

[a] *P* value by Wilcoxon rank sum, 2-sample *t* test, Chi-square, or Fisher's exact test, as appropriate.

[b] The included participants had detectable viremia on ≥2 samples in the first 3 months after transplant and had a Month 4 blood sample to assess for viral clearance. Clearance was defined as having undetectable viremia at Month 4.

Table 7. BK Polyomavirus Viremia Clearance by Month 4 and Enzyme-linked Immune Absorbent Spot Results

Participant	Month 1 Viremia Copies/mL	Month 2 Viremia Copies/mL	Month 3 Viremia Copies/mL	Month 3 ELISPOT Spots Above Control	Month 4 Viremia Copies/mL
Cleared viremia					
1	2000	7600	3400	0	0
2	417	168	0	2.9	0
3	1200	51	0	20.4	0
4	3000	500	0	149	0
5	0	6800	196	7	0
6	190	5300	600	65.7	0
7	0	1100	900	44.3	0
8	38	102	0	3.3	0
9	700	172	0	1.7	0
10	5900	11 900	8700	0	0
11	No sample	201	185	1.9	0
12	1 300 000	58 700	98	127.3	0
13	0	2900	148	82.5	0
14	2400	2100	0	48.5	0
15	4200	1500	0	38.2	0
16	16 100	316	0	26.3	0
17	67	1600	1100	19.8	0
18	1300	70	0	14.3	0
Did not clear viremia					
1	175	1200	0	0	89
2	1400	26 500	10 400	8.4	109
3	1300	7200	900	153.6	193
4	900	500	429	14.5	800
5	0	1400	339	2.1	1000
6	1100	23 300	42 500	0	2700
7	1700	600	700	1.6	2800
8	900	2100	66 400	0	2900
9	38	No sample	35 000	0	3100
10	800	700	1700	17.4	3300
11	1700	57 500	166 000	.8	3600
12	6400	60 000	800	40.3	4000
13	3000	900	7300	0	5500
14	222	1300	5700	0	6700
15	1500	12 900	93 000	1.3	13 500
16	209	3900	16 400	0	23 500
17	4700	8500	27 800	−3.8	34 500
18	900	21 600	48 800	4.1	57 400
19	600	3600	25 700	1.2	68 900
20	800	1100	1900	−1.7	97 000
21	184 000	496 000	2 000 000	5.9	460 000
22	No sample	574 000	682 000	−1.3	463 000
23	79 900	2 700 000	8 500 000	8.2	1 400 000
24	87	73 000	168 000	22.3	2 400 000
25	26 100	287 000	14 000 000	64.9	13 000 000

These 43 selected participants had persistent viremia in the first 3 months after transplant, had a Month 4 sample to assess for clearance, and had a Month 3 ELISPOT result. Participants with peak viremia <10 000 copies/mL and ELISPOT counts >10 above the negative control (bold and highlighted) were more likely to clear viremia by Month 4.

Abbreviation: ELISPOT, enzyme-linked immune absorbent spot.

mortality among 400 HCT recipients. The incidence of BKPyV viremia was 54%, most episodes were persistent, and, similar to our findings, viremia was associated with mortality. BKPyV viremia occurred a median of 10 days before cystitis. Others have reported that viremia or viruria predict cystitis, which we also confirmed [3, 6].

About 25% of our cohort developed cystitis [5, 7, 11]. BKPyV viremia was associated with a higher risk of receiving dialysis and an eGFR that was, on average, 20 ml/min/1.73m^2 lower by 2 years after transplant. O'Donnell et al [27] monitored 57 adults after HCT and observed that viremia was independently associated with higher peak creatinine, similar to retrospective

studies in children [4]. In contrast to antithymocyte globulin, alemtuzumab was not associated with the risk of BKPyV replication. It is possible that these data are confounded by an unmeasured variable or that qualitative, BKPyV-specific T-cell recovery after alemtuzumab is importantly different than recovery after antithymocyte globulin.

Although we and others have shown that BKPyV viremia can predict cystitis, the positive predictive value of viremia remains low, implying that other factors, perhaps related to the host response or viral diversity, are important to determining which patients will develop disease [11]. We observed that BKPyV viremia was associated with dialysis, TMA, acute GVHD, and death. More research is needed to determine whether these associations are causal, time-dependent, associated with poor immune reconstitution, or are confounded by higher degrees of immunosuppression. In vitro studies indicate that BKPyV infection can induce host endothelial cell production of interferon [28], which may precipitate both TMA and acute GVHD, supporting a possible direct, causative effect of BKPyV viremia on these other, significant posttransplant complications [7].

The strengths of our approach include the multi-center design, collection of samples and clinical data for 2 years after transplant, and centralized lab testing. We assessed both the humoral and cellular host immune response to BKPyV. Finally, we examined the association between BKPyV replication and eGFR for the first time in the HCT population using both serum creatinine and cystatin C, which has advantages in patients with decreased muscle mass [10]. Participants with viremia >10 000 copies/mL had an 18–26% decrease in baseline eGFR by 2 years post-HCT (Table 5). In older adults, a 30% reduction in eGFR over 2 years has been strongly associated with end-stage kidney disease and death [29]. While similar data are not available in children, it is plausible that the eGFR decline we observed would also be associated with poor outcomes in a younger population. Our study was limited by a lack of biopsy data to confirm nephropathy. Nevertheless, BKPyV viremia ≥10 000 copies/mL has been classified as presumptive nephropathy after kidney transplantation, even without a biopsy [30]. Patient characteristics, most notably the high proportion of nonmalignant indications, may not reflect the risk for BKPyV infection at other centers. Not all centers have the resources to perform centralized, quantitative testing for viremia, and semiquantitative detection of high-level viremia may have produced the same observations. Our monthly sampling frequency may have missed earlier windows of detection associated with clinical outcomes, including TMA and GVHD. The potential benefits and risks of treatments, such as intravenous immune globulin and cidofovir, would need to be tested in randomized trials. Finally, clinical information was abstracted from the medical record, possibly influencing the capture of outcomes, such as cystitis and GVHD.

In conclusion, BKPyV viremia was associated with significant kidney and bladder disease and mortality after HCT. Moreover, asymptomatic viremia was common and was associated with decreased kidney function. Assessments of novel interventions, such as the infusion of virus-specific T cells, are needed to determine whether preventing or treating BKPyV infection can improve morbidity and mortality, as our study does not suggest the utility of cidofovir. Patients with persistent, high-level symptomatic or asymptomatic viremia may benefit from infusion of BKPyV-specific T cells, and this hypothesis can be tested in future clinical trials.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgement. The authors thank Dr Ulf Beier for his assistance with illustrating the figures.

Financial support. This work was supported by the National Institute of Diabetes and Digestive and Kidney Diseases at the National Institutes of Health (grant numbers K23 DK101600 to B. L. L. and K23 DK093556 to M. R. D.) and the National Center for Advancing Translational Sciences (grant number UL1 TR001878). Viracor-Eurofins tested the samples for BK polyomavirus viremia, viruria, and antibody at no charge.

Potential conflicts of interest. B. L. L and S. J. are coinventors of a patent application under review: Compositions and Methods for Treatment of HSCT-Associated Thrombotic Microangiopathy (United States Patent Number PCT/US2014/055922, 2014). B. L. L. has received consulting fees from Jazz Pharmaceuticals and Bioporto. S. K. and M. A. are employees of Viracor-Eurofins. M. R. D. has received research funding from Mallinckrodt, unrelated to this study. S. M. D. has received research support from Alexion Pharmaceuticals, personal fees from Novartis and Anthem, and research grants from Prolacta, outside the submitted work. S. J. has received research support from Alexion Pharmaceuticals; has received grants from the National Institutes of Health; has received personal fees from Omeros, Arcus Medica, and Magnolia Innovations, outside the submitted work; and has the following patents pending: 61/878,119, 62/094,802, 62/172,987, and 62/593,401. T. O. has received personal fees from Bluebird Bio, Miltenyi, and Novartis, outside the submitted work. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Hirsch HH, Knowles W, Dickenmann M, et al. Prospective study of polyomavirus type BK replication and nephropathy in renal-transplant recipients. N Engl J Med **2002**; 347:488–96.
2. Bedi A, Miller CB, Hanson JL, et al. Association of BK virus with failure of prophylaxis against hemorrhagic cystitis following bone marrow transplantation. J Clin Oncol **1995**; 13:1103–9.
3. Cesaro S, Tridello G, Pillon M, et al. A prospective study on the predictive value of plasma BK virus-DNA load for hemorrhagic cystitis in pediatric patients after stem cell transplantation. J Pediatric Infect Dis Soc **2015**; 4:134–42.
4. Haines HL, Laskin BL, Goebel J, et al. Blood, and not urine, BK viral load predicts renal outcome in children with hemorrhagic cystitis following hematopoietic stem cell transplantation. Biol Blood Marrow Transplant **2011**; 17:1512–9.
5. Cesaro S, Dalianis T, Hanssen Rinaldo C, et al; European Conference on Infections in Leukemia (ECIL)-6 Group. ECIL guidelines for the prevention, diagnosis and treatment of BK polyomavirus-associated haemorrhagic cystitis in haematopoietic stem cell transplant recipients. J Antimicrob Chemother **2018**; 73:12–21.

6. Erard V, Kim HW, Corey L, et al. BK DNA viral load in plasma: evidence for an association with hemorrhagic cystitis in allogeneic hematopoietic cell transplant recipients. Blood **2005**; 106:1130–2.
7. Hill JA, Mayer BT, Xie H, et al. The cumulative burden of double-stranded DNA virus detection after allogeneic HCT is associated with increased mortality. Blood **2017**; 129:2316–25.
8. Hill JA, Mayer BT, Xie H, et al. Kinetics of double-stranded DNA viremia after allogeneic hematopoietic cell transplantation. Clin Infect Dis **2018**; 66:368–75.
9. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant **2009**; 15:1143–238.
10. Laskin BL, Nehus E, Goebel J, Furth S, Davies SM, Jodele S. Estimated versus measured glomerular filtration rate in children before hematopoietic cell transplantation. Biol Blood Marrow Transplant **2014**; 20:2056–61.
11. Hayden RT, Gu Z, Liu W, et al. Risk factors for hemorrhagic cystitis in pediatric allogeneic hematopoietic stem cell transplant recipients. Transpl Infect Dis **2015**; 17:234–41.
12. Wong AS, Chan KH, Cheng VC, Yuen KY, Kwong YL, Leung AY. Relationship of pretransplantation polyoma BK virus serologic findings and BK viral reactivation after hematopoietic stem cell transplantation. Clin Infect Dis **2007**; 44:830–7.
13. Schwartz GJ, Schneider MF, Maier PS, et al. Improved equations estimating GFR in children with chronic kidney disease using an immunonephelometric determination of cystatin C. Kidney Int **2012**; 82:445–53.
14. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med **2012**; 367:20–9.
15. Jodele S, Davies SM, Lane A, et al. Diagnostic and risk criteria for HSCT-associated thrombotic microangiopathy: a study in children and young adults. Blood **2014**; 124:645–53.
16. Leboeuf C, Wilk S, Achermann R, et al. BK polyomavirus-specific 9mer CD8 T cell responses correlate with clearance of BK viremia in kidney transplant recipients: first report from the swiss transplant cohort study. Am J Transplant **2017**; 17:2591–600.
17. Ginevri F, Azzi A, Hirsch HH, et al. Prospective monitoring of polyomavirus BK replication and impact of pre-emptive intervention in pediatric kidney recipients. Am J Transplant **2007**; 7:2727–35.
18. Schachtner T, Müller K, Stein M, et al. BK virus-specific immunity kinetics: a predictor of recovery from polyomavirus BK-associated nephropathy. Am J Transplant **2011**; 11:2443–52.
19. Schaenman JM, Korin Y, Sidwell T, et al. Increased frequency of BK virus-specific polyfunctional CD8+ T cells predict successful control of BK viremia after kidney transplantation. Transplantation **2017**; 101:1479–87.
20. Apiwattanakul N, Hongeng S, Anurathapan U, et al. Viral-specific T-cell response in hemorrhagic cystitis after haploidentical donor stem cell transplantation. Transpl Infect Dis **2017**; 19:e12775. doi: 10.1111/tid.12775.
21. Schneidawind D, Schmitt A, Wiesneth M, et al. Polyomavirus BK-specific CD8+ T cell responses in patients after allogeneic stem cell transplant. Leuk Lymphoma **2010**; 51:1055–62.
22. Saliba RM, Rezvani K, Leen A, et al. General and virus-specific immune cell reconstitution after double cord blood transplantation. Biol Blood Marrow Transplant **2015**; 21:1284–90.
23. Tzannou I, Papadopoulou A, Naik S, et al. Off-the-shelf virus-specific T cells to treat BK virus, human herpesvirus 6, cytomegalovirus, Epstein-Barr virus, and adenovirus infections after allogeneic hematopoietic stem-cell transplantation. J Clin Oncol **2017**; 35:3547–57.
24. Pello OM, Innes AJ, Bradshaw A, et al. BKV-specific T cells in the treatment of severe refractory haemorrhagic cystitis after HLA-haploidentical haematopoietic cell transplantation. Eur J Haematol **2017**; 98:632–4.
25. Papadopoulou A, Gerdemann U, Katari UL, et al. Activity of broad-spectrum T cells as treatment for AdV, EBV, CMV, BKV, and HHV6 infections after HSCT. Sci Transl Med **2014**; 6:242ra83.
26. Lee YJ, Zheng J, Kolitsopoulos Y, et al. Relationship of BK polyoma virus (BKV) in the urine with hemorrhagic cystitis and renal function in recipients of T Cell-depleted peripheral blood and cord blood stem cell transplantations. Biol Blood Marrow Transplant **2014**; 20:1204–10.
27. O'Donnell PH, Swanson K, Josephson MA, et al. BK virus infection is associated with hematuria and renal impairment in recipients of allogeneic hematopoetic stem cell transplants. Biol Blood Marrow Transplant **2009**; 15: 1038–48 e1.
28. An P, Sáenz Robles MT, Duray AM, Cantalupo PG, Pipas JM. Human polyomavirus BKV infection of endothelial cells results in interferon pathway induction and persistence. PLOS Pathog **2019**; 15:e1007505.
29. Coresh J, Turin TC, Matsushita K, et al. Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. JAMA **2014**; 311:2518–31.
30. Hirsch HH, Randhawa P. BK polyomavirus in solid organ transplantation. Am J Transplant **2013**; 13(Suppl 4):179–88.