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ORIGINAL ARTICLE

Implementing a regional standardized BK polyomavirus screening protocol across eleven transplant centres

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SUMMARY

BK polyomavirus (BKPyV) reactivation is regularly monitored after kidney transplant to prevent progression to BK associated nephropathy (BKAN). The New England BK Consortium, made up of 12 transplant centres in the northeastern United States, conducted a quality improvement project to examine adherence to an agreed upon protocol for BKPyV screening for kidney transplants performed in calendar years 2016–2017. In a total of 1047 kidney transplant recipients (KTR) from 11 transplant centres, 204 (19%) had BKPyV infection, defined as detection of BKPyV in plasma, with 41 (4%) KTR progressing to BKAN, defined by either evidence on biopsy tissues or as determined by treating nephrologists. BKPyV infection was treated with reduction of immune suppressants (RIS) in >70% of the patients in all but two centres. There was no graft loss because of BKAN during the two-year follow-up. There were nine cases of post-RIS acute rejection detected during this same period. Adherence to the protocol was low with 54% at 12 months and 38% at 24 months, reflecting challenges of managing transplant patients at all centres. The adherence rate was positively correlated to increased detection of BKPyV infection and was unexpectedly positively correlated to an increase in diagnosis of BKAN.

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Introduction

The human BK polyomavirus (BKPyV) is a ubiquitous virus which causes a persistent and most often clinically inapparent infection of the uroepithelium and renal tubule cells in healthy individuals with seroprevalence of 60–70% worldwide [1]. This pathogen gains more relevance in some immunocompromised individuals, including in particular kidney transplant recipients (KTRs) where inadequate control of viral replication by a suppressed immune response can lead to BKPyV-associated nephropathy (BKAN), resulting in loss of the graft in up to 5% of the KTRs [2]. In this setting, KTRs with progressive BKPyV infection generally remain asymptomatic and have historically presented to care with non-specific worsening of allograft function after BKAN had already developed. Given the poor short- and long-term allograft outcomes associated with BKAN and lack of an antiviral treatment for BKPyV, early detection of viral presence in urine or blood remains the crucial means to prevent BKAN.

Various screening and preemptive immune suppression reduction strategies for BKPyV infection are used by transplant centres in an effort to reduce the incidence and clinical impact of BKAN, mostly following the recent American Society of Transplantation (AST) screening guidelines (qualitative nucleic acid test on blood monthly until month 9 after transplant and then every 3 months until 2 years after transplant) [3]. Screening protocols for BKPyV infection in KTRs employ various direct or indirect tests to detect the virus in plasma or urine samples, comprised most commonly of qualitative or quantitative nucleic acid testing or urine cytology, each with diagnostic characteristics and associated costs which impact individual transplant centre's choice of screening test. One limitation common to all these tests is adequate sensitivity and specificity to predict whether a patient with BKPyV infection will subsequently develop BKAN. While some factors such a high level or long duration of DNAemia may predict subsequent BKAN, quantitative viral load testing is not yet standardized between centres and duration of DNAemia is difficult to predict prospectively. AST guidelines suggest. The standard of care treatment for BKPyV infection at present entails reduction of immunosuppression (RIS), which makes an accurate risk prediction imperative, since RIS may in turn also cause short- or long-term damage to the allograft by increasing graft rejection risk. Given that the overall goal of screening and preemptive treatment is to reduce BKAN incidence and severity rather than treat BKPyV infection (which often remains clinically silent even among KTRs), the optimal strategy for screening remains unclear. Also, even with a planned screening protocol, adherence success is challenging given that screening for BK is not usually part of the patient's standing lab tests that are done most frequently. No studies have been done to date to evaluate screening adherence on this scale.

The New England BK Consortium (NEBKCON) is an ongoing collaboration between participating transplant centres in United Network for Organ Sharing (UNOS) Region 1 (composed of 14 independent transplant centres) with members engaged in ongoing efforts to improve the management of BKPyV infection in KTRs. In 2015, participating centres first identified the need to improve screening for BKPyV reactivation when the consortium determined that screening protocols were different amongst the 11 participating centres [4]. Furthermore, NEBKCON conducted a survey of AST members and discovered that amongst 64 US and international centres, screening practices differed and that there was no existing metrics to measure adherences to the screening protocols [5]. Thus, NEBKCON members agreed upon a standardized screening protocol for BKPyV infection, which was then implemented by 11 centres, as a first step to ultimately improve screening of BKPyV in KTRs. Here, we report the implementation of this quality improvement study to evaluate each centres adherence to this protocol, which also provides an updated description of early clinical outcomes after BKPyV infection with current immunosuppressive regimens and BKPyV infection management strategies.

Patients and methods

All member centres of NEBKCON were invited to participate in this quality improvement initiative; no institutional review board (IRB) review was required by the institutions owing to the study comprising quality improvement efforts rather than human subjects research. Each centre provided de-identified information on KTRs who received kidney transplants at their centres during calendar years 2016 and 2017 for the

analysis. Data was obtained by individual chart review and extraction into a standardized data collection form. KTRs were excluded from the analysis if in addition, they also had a non-abdominal transplant (i.e. heart or lung), if they had primary graft non-function, or if they were lost to follow-up prior to post-transplant month 12. Data extraction took place at various centres throughout calendar years 2019–2021 and included at least 2 years of clinical follow-up after transplantation.

The NEBKCON BKPyV screening protocol was agreed upon by consensus and entails screening for BKPyV infection, by either urine qualitative PCR (qPCR) or plasma qPCR, once monthly for the first 6 months after transplantation and then once every 3 months for 18 months thereafter, at a minimum. Adherence to this screening protocol was measured by comparing whether an individual KTR had the appropriate number and timing of BKPyV screening tests as compared with the protocol; only those individuals with 100% compliance with the screening protocol were considered adherent. 12-month adherence was defined as adherent until BKPyV infection was detected, the kidney allograft was lost, death or at least 12 months after transplantation. 24-month adherence was defined as adherent until BKPyV infection was detected, the kidney allograft was lost, death or loss to follow-up or at least 24 months after transplantation. BKPyV infection was defined as any detectable and quantifiable viremia (the presence of viriuria alone was not sufficient to define an infection for those centres using urine qPCR as a screening assay). BKAN was defined by either by clinical assessment or by concordant biopsy findings. Data extraction was performed by retrospective chart review at the participating centres. Correlation of adherences to BKPyV viremia and BKAN were calculated using two-tail mid-P exact methods.

Results

Eleven participating transplant centres adapted and attempted to implement the standardized screening protocol at the start of 2016. Data were collected to include at minimum two-years of follow-up data on a total of 1047 KTRs (Table 1). Adherence to at least 12 months of the NEBKCON screening protocol was 54%, with individual centres reporting rates between 11% and 96% (Table 2). Adherence to 24 months of the NEBKCON screening protocol was 38%, with individual centres reporting rates between 4% and 69%. The overall rate of BKAN associated with BKPyV infection was similar between all KTRs with BKPyV infection (20%), those adherent to at least 12 months of screening (18%) and those adherent to 24 months of screening (17%). Adherence to 12 and 24 months of the screening protocol was associated with an increased rate of detected BKPyV infection [26% vs. 12% ($P < 1 \times 10^{-7}$) and 32% vs. 12% ($P < 1 \times 10^{-7}$), respectively] as well as an increased rate of detected BKAN [5% vs. 3% ($P = 0.24$) and 6% vs. 3% ($P = 0.04$), respectively] (Table 3).

There were 204 (19%) detected cases of BKPyV infection among the 1047 KTRs screened, with individual centres reporting rates between 4% and 38%.

Table 1. BKPyV incidence, management and clinical course.

Center	*N*	BKPyV (%*N*)	BKAN (%*N*)	RIS (%V)	IVIG (%V)	Steroid (%V)	Early allograft loss (%V)	Early post-treatment rejection (%V)
A	56	2 (4)	0	2 (100)	0	0	0	0
B	87	21 (24)	3 (3)	20 (95)	1 (5)	0	0	1 (5)
C	102	15 (15)	3 (3)	14 (93)	7 (47)	2 (13)	0	0
D	54	9 (17)	1 (2)	7 (78)	1 (11)	1 (11)	0	0
E	101	29 (29)	3 (3)	12 (41)	0	0	0	2 (7)
F	32	12 (38)	2 (6)	12 (100)	2 (17)	0	0	1 (8)
G	168	28 (17)	6 (4)	27 (96)	8 (29)	0	0	1 (4)
H	141	15 (11)	12 (9)	13 (87)	2 (13)	4 (27)	0	2 (13)
I	87	20 (23)	5 (6)	5 (25)	2 (10)	1 (5)	0	0
J	121	39 (32)	5 (4)	31 (79)	3 (8)	8 (21)	0	1 (3)
K	98	14 (14)	1 (7)	10 (71)	2 (14)	0	0	1 (7)
Total	1047	204 (19)	41 (4)	153 (75)	28 (14)	16 (8)	0 (0)	9 (4)

BKAN, BKPyV associated nephropathy; BKPyV, BK polyomavirus; IVIG, intravenous immunoglobulin; *N*, number of kidney transplant recipients monitored during study period; RIS, reduction in immunosuppression; V, number of kidney transplant recipients with BKPyV DNAemia.

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Table 2. Screening adherence and incidence of BKAN.

Centre	BKAN (%V)	Ad12 (%*N*)	Ad12 + BKAN (%Ad12V)	Ad24 (%*N*)	Ad24 + BKAN (%Ad24V)
A	0	43 (77)	0	21 (38)	0
B	3 (14)	58 (67)	3 (14)	51 (59)	3 (14)
C	3 (20)	69 (68)	3 (23)	51 (50)	2 (20)
D	1 (11)	41 (76)	1 (11)	22 (41)	1 (33)
E	3 (10)	54 (53)	2 (11)	26 (26)	2 (11)
F	2 (17)	21 (66)	2 (22)	19 (59)	2 (22)
G	6 (21)	30 (18)	1 (9)	17 (10)	1 (9)
H	12 (80)	16 (11)	4 (100)	6 (4)	2 (100)
I	5 (25)	60 (69)	4 (29)	60 (69)	4 (29)
J	5 (13)	83 (69)	5 (17)	64 (53)	4 (17)
K	1 (7)	94 (96)	1 (7)	63 (64)	1 (8)
Total	41 (20)	569 (54)	26 (18)	400 (38)	22 (17)

Ad12, number of kidney transplant recipients adherent to BKPyV screening for at least 12 months; Ad12V, number of kidney transplant recipients adherent to BKPyV screening for at least 12 months with BKPyV DNAemia; Ad24, number of kidney transplant recipients adherent to BKPyV screening for 24 months; Ad24V, number of kidney transplant recipients adherent to BKPyV screening for 24 months with BKPyV DNAemia; BKAN, BKPyV-associated nephropathy; BKPyV, BK polyomavirus; *N*, number of kidney transplant recipients monitored during study period; V, number of kidney transplant recipients with BKPyV DNAemia.

Table 3. Correlation of BKPyV and BKAN with screening adherence.

	N	BKPyV (%*N*)	Significance	BKAN (%*N*)	Significance
Adh12 (Y)	569	146 (26)	$P < 1 \times 10^{-7}$	26 (5)	$P = 0.24$
Adh12 (N)	478	58 (12)		15 (3)	
Adh24 (Y)	400	128 (32)	$P < 1 \times 10^{-7}$	22 (6)	$P = 0.04$
Adh24 (N)	647	76 (12)		19 (3)	

Ad12, number of kidney transplant recipients adherent to BKPyV screening for at least 12 months; Ad24, number of kidney transplant recipients adherent to BKPyV screening for 24 months; BKAN, BKPyV-associated nephropathy; BKPyV, BK polyomavirus; *N*, number of kidney transplant recipients monitored during study period.

Additionally, there were 41 (4%) detected cases of BKAN, with individual centres reporting rates between 0% and 9%. BKPyV infection was detected a mean of 120 days after transplant and a mean of 35 days after the last negative screening test (data not shown). Mean initial viral load detected was similar between individuals with and without 12-month adherence to the screening protocol (25 100 and 27 600 copy/ml, respectively: data not shown). All centres except two treated more than 70% of detected BKPyV infections with RIS; four centres treated more than 95% of detected BKPyV infections with RIS. IVIG (14%) and corticosteroids (8%) were used sparingly in the treatment of BKPyV infection. While there was no early allograft loss because of BKPyV infection, there were nine cases of early post-treatment acute allograft rejection. Centres used various medications for induction immunosuppression, but all typically used three-agent maintenance immunosuppression; more than half reported using an early steroid taper protocol (Table 4). A variety of BKPyV qPCR assays were used, with some centres using an in-house assay not available elsewhere. Most centres used plasma qPCR for their primary screening assay, though two used urine qPCR as the initial screening assay with a reflex to plasma qPCR if urine was positive.

Discussion

This study leverages an ongoing collaboration between 11 transplant centres in the northeastern United States to understand how well each centre could implement a standardized screening protocol for BKPyV in KTRs, as a first step in improving post-transplant patient care by reducing allograft damages or loss because of BKPyV infection. We measured and analyzed adherence to a standardized screening protocol for BKPyV infection with respect to subsequent BKPyV-related infectious and non-infectious clinical events. In addition, we provided an updated account of the incidence and early clinical outcomes of BKPyV infection after kidney transplant associated with contemporary immunosuppressive across 11 different transplant centres.

Through this study, we discovered that not only does each transplant centre collect different specimen types (blood or urine) and use different time points to conduct the screen, but also that the adherence rate to screening for BKPyV post KT varies greatly between centers with a low average rate of 54% at 12 months and further decrease to 18% at 24 months. These results may be because of several factors, including that most screening tests are performed locally closer to the KTR, the need for personnel support to conduct the screening tests and the lack of previously established ongoing QI assessments.

Interestingly, in this study, we demonstrated not only an increased rate of BKPyV infection in those patients who were adherent to the screening protocol but also an increased rate of BKAN. We hypothesized prior to

Table 4. Typical immunosuppression and BKPyV screening practices during study period.

Center	Induction	Maintenance	Early steroid taper	BKPyV qPCR assay	Screening method	Screening frequency (months)
A	Alemtuzuma†	T/M/P	Y	In house	U → P	q1 ×6, q3 ×18
B	ATG	T/M/P	N	‡	P	q1 ×6, q3 ×18
C	ATG	T/M/P	Y	§	U → P	q1 ×6, q3 ×18
D	Alemtuzuma†	T/M/P	Y	In house	P	q1 ×12, q3 ×12
E	Basiliximа†	T/M/P	N	¶	P	q1 ×6, q3 ×18
F	ATG	T/M/P	Y	In house	P	q1 ×12, q2 ×12
G	ATG	T/M/P	N	§	P	q1 ×6, q2 ×18
H	Various*	T/M/P	Y	§	P	Various†
I	ATG	T/M/P	Y	§	P	q1 ×6, q3 ×18
J	ATG	T/M/P	Y	In house	P	q1 ×6, q3 ×18
K	Alemtuzuma†	T/M/P	N	§	P	q1 ×6, q3 ×18

ATG, anti-thymocyte globulin; BKPyV, BK polyomavirus; P, plasma qPCR; T/M/P, tacrolimus, mycophenolate, prednisone; U → P, urine qPCR with reflex to plasma qPCR.

*Typical induction immunosuppression practices changed at this centre during the study period.

†No standardized screening protocol was in place during study period at this centre, instead screening frequency was at the discretion of the treating physician.

‡Commercial laboratory 1.

§Commercial laboratory 2.

¶Commercial laboratory 3.

data analysis that those patients who were not adherent to the screening protocol might have relatively higher rates of BKAN given the potential for BKPyV infection to progress undetected for longer in this population; instead, we saw the opposite. It is not surprising to find an increased rate of BKPyV infection detected in concert with more frequent screening, but the difference in rates of BKAN depending on the patient's adherence to the screening protocol suggests either underdiagnosis of BKAN in patients not adherent to the screening protocol or overdiagnosis of BKAN in patients who were adherent. Underdiagnosis of BKAN in the nonadherent cohort seems somewhat less likely since the overwhelming majority of these patients were still screened for BKPyV infection (albeit somewhat less) frequently and thus presumably would have eventually had BKPyV infection detected if they were to have developed BKAN. This is likely true, given that there were similar rates of BKAN among those with detected BKPyV infection independent of whether or not they were adherent to the protocol. The opposite scenario (overdiagnosis of BKAN in the adherent cohort) cannot be definitively established in retrospect. While the overall rates of measurable clinical outcomes in this study (allograft loss to BKAN, acute rejection after BKPyV infection) were good as compared with historical cohorts, as with any screening protocol, it is worth considering the overall net effect of the described screening protocol given the potential short- and long-term clinical implications of RIS for any KTR and the impact that adherence to a screening protocol may have on differential rates of BKAN diagnosis (and ensuing RIS).

This quality analysis reveals the difficulty in implementing a standardized protocol in a localized area of the United States, though clinical practice and obstacles to improving post KTR care may share many similarities with other regions in the United States and internationally. Furthermore, there was no available data on adherence to screening prior to implementation. Thus, our measured adherence may already be improved from prior by this implementation. In addition, the true incidence of BKAN reported in this study may be obscured by the low rate of biopsies after BKPyV infection, however the uniform definition for BKAN used by participating centres during retrospective chart review allowed for a consistent measure throughout the study. The true incidence of allograft loss after BKAN or rejection after BKPyV infection may have been underreported because of the relatively short two-year clinical follow-up after detection of infection, though even within this timeframe we were able to detect a sizeable number of events.

The strength of the quality improvement project is that it was conducted in the entire geographical region

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with participation from 11 different centres, which provides a comprehensive understanding of adherence to screening practices, given the differences in patient and staff sizes and clinical follow up frequencies. Our goal is for each participating centre to take this data back to their programmes to address their unique screening adherence barriers. Based on these data, the consortium is poised to improve post kidney transplant patient care by specifically improving BKPyV screening test adherence.

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Conflicts of interest

The authors of this manuscript have no conflicts of interest to disclose.

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Data availability statement

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

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