Screening and Management Practices for Polyoma (BK) Viremia and Nephropathy in Kidney Transplant Recipients From the Lands Down Under: Addressing the Unknowns and Rationale for a Multicenter Clinical Trial

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BK polyomavirus infection in transplanted kidneys that leads to BK virus–associated nephropathy (BKVAN) is an important cause of allograft loss and has limited treatment options.[1] Recent data suggest that BK viremia affects approximately 10% of people within the first 12 months following kidney transplantation.[2] Among recipients with BKVAN, the overall risk of allograft loss is substantially increased, estimated to be 50% within 5 years of diagnosis. Geographic variation in the rates of BK infection also has been recognized. Depending on local epidemiology and immunosuppression practices, the prevalence of viruria, viremia, and histological features of BKVAN is reported to be between 35% and 40%, 12% and 15%, and 3% and 8%, respectively.[3]

Early detection of BK viremia through screening may allow judicious reduction in immunosuppression dose preventing the detrimental effects of BKVAN, such as premature allograft loss. Current screening methods are highly variable between centers and include a combination of quantitative detection of BK DNA in whole blood (BK viremia) using real-time polymerase chain reaction assay or the detection of BK viruria. The Kidney Disease Improving Global Outcomes 2009 guidelines for the care of kidney transplant recipients recommended routine monthly screening for BK viremia using BK nucleic acid testing for the first 3 to 6 months and then 3 monthly thereafter for the first year post transplantation.[4]

Observational data also suggest a higher number of BK copies detected (BK viral load) is associated with an increased risk of BKVAN. Prior studies have indicated a test threshold of 1×10^4 viral copies per milliliter has a test specificity and sensitivity for BKVAN of 95.0 (77.5–99.7) and 83.4 (78.4–84.7), respectively, with positive and negative predictive values of 61.9 (50.5–64.9) and 98.3 (92.4–99.9), assuming an overall prevalence of 5%.[5] A single-center study reported reduction in immunosuppression may result in decrease in the BK viral load and a concomitant decrease in the risk of BKVAN,[6] but the optimal treatment strategies are uncertain. Trials of prophylactic treatment with quinolones also showed

Table 1. Baseline characteristics of the survey participants

Demographics, *n* (%)	*N* = 113
Male	71 (63)
Female	38 (34)
Prefer not to say	4 (3)
Age groups in years, *n* (%)	
20–29	4 (3.5)
30–39	27 (23.9)
40–49	39 (34.5)
50–59	35 (31.0)
≥ 60	8 (7.1)
State/Territory[a]	
Australian Capital Territory	4 (4.4)
New South Wales	39 (43.3)
Northern Territory	3 (3.3)
Queensland	15 (16.7)
South Australia	4 (4.4)
Tasmania	1 (1.2)
Victoria	19 (21.1)
West Australia	5 (5.6)
Years of practicing as a nephrologist	
1–5	34 (30.1)
6–10	12 (11.4)
11–15	19 (16.8)
>15	47 (41.6)
Country of practice	
Australia	93 (82.3)
New Zealand	20 (17.7)
Transplanting unit[b]	
Yes	68 (62.4)
No	41 (37.6)

[a]*n* = 23 did not provide details of which states they reside in.
[b]*n* = 4 did not provide details of their practice location.

lack of treatment efficacy in the prevention of disease.[7] The current options include complete withdrawal of the antimetabolites, or switching from mycophenolate mofetil (MMF) to azathioprine, 50% dose reduction in calcineurin inhibitors, conversion from tacrolimus to ciclosporin, introduction of mammalian target of rapamycin inhibitors, or replace antimetabolite agents with leflunomide.[1] Once BKVAN develops, current treatment regimens are limited and largely unproven, beyond reducing the intensity of immunosuppression, as described previously. Recent work has shown possible benefits in the clearance of BK viruses from blood and renal tissues with i.v.Ig and the antiviral agent cidofovir, but this is limited to a single-center study.[2] To better understand the current screening and management patterns for BK viremia and BKVAN, and to inform the design of a multicenter randomized controlled intervention trial in the management of BK infection in kidney transplant recipients, we conducted a survey among relevant Australian and New Zealand clinicians.

RESULTS

Of the 557 practicing nephrologists in Australia and New Zealand, 113 (20.2%) completed the survey. The

baseline characteristics of the respondents are shown in Table 1. Most respondents were men (*n* = 73, 61%), aged 40 years and older (*n* = 82, 72.6%), had more than 10 years of experience in nephrology (*n* = 66, 58.4%), worked in a transplanting unit (*n* = 68, 62.4%), and lived in Australia (*n* = 93, 82.3%). The Australian and New Zealand Society of Nephrology and the Transplantation Society of Australia and New Zealand male membership is approximately 55% to 60%. This is consistent with the gender distribution of the survey.

Reported 1-Year Incidence of BK Viremia and BKVAN in Kidney Transplant Recipients

Table 2 shows the reported incidence, screening, and management strategies of BK infection in kidney transplant recipients. Approximately 50% of respondents reported an estimated incidence of BK viremia of approximately 10% to 20% and 1% to 3% for BKVAN.

Screening Practices for BK Viremia

There was substantial variability in reported screening practices. The most common screening modality was BK quantitative real-time polymerase chain reaction on plasma (80%). The use of urine viruria and decoy cells was much less frequent (less than 10%). The frequency of screening varied between monthly (27%) to 3-monthly (18%) within the first 12 months of transplantation, typically with more frequent screening in the first 3 months posttransplant. Approximately 10% of nephrologists stated they do not routinely perform screening; however, once persistent viremia was detected, 30% would perform allograft biopsy to exclude BKVAN, whereas most (approximately 70%) would consider a biopsy only when graft dysfunction occurred.

Management Strategies of BK Viremia and BKVAN

Most respondents reported that they would reduce the dose of immunosuppressive drugs (70%) in recipients with persistent BK viremia. Reduction in the doses of calcineurin inhibitors and antimetabolites (such as MMF) was the first-line practice for most respondents (*n* = 75, 66.4%), followed by a switch to alternative calcineurin inhibitors (tacrolimus to cyclosporine) and antimetabolite therapy (such from MMF to leflunomide, or MMF to azathioprine) (*n* = 34, 30%), then changing from MMF to leflunomide (*n* = 30, 26.5%) without altering calcineurin inhibitor doses, followed by alteration to a combination of low-dose tacrolimus and mammalian target of rapamycin inhibitors (*n* = 9, 8%). Once BKVAN developed, a range of adjuvant treatment options were available to the respondents. Cidofovir

Table 2. Reported incidence, screening, and management strategies of BK viral infection in kidney transplant recipients ($n = 113$)

Incidence of BK viremia, n (%)	
< 10%	42 (37.2)
10–15%	48 (42.5)
16–20%	9 (7.9)
>20%	4 (3.5)
No response	10 (8.9)
Incidence of BKVAN, n (%)	
<1%	20 (17.7)
1–3%	70 (62)
>3%	12 (10.6)
No response	11 (9.7)
Frequency of screening, n (%)	
Monthly	30 (26.6)
Every second month	10 (8.6)
Every 3 months	20 (17.7)
Every 6 months	2 (1.8)
Never	12 (10.6)
Other	29 (25.7)
No response	10 (8.9)
Types of screening, n (%)[a]	
Urine decoy cells	6 (5.3)
Real-time plasma BK polymerase chain reaction	90 (80)
Urinary viral load	14 (12.3)
Performance of kidney biopsy to exclude BKVAN, n (%)[a]	
Presence of viruria and no viremia	0 (0)
Presence of viremia only	29 (25.7)
Presence of graft dysfunction	78 (69)
Presence of graft dysfunction and viremia	80 (71)
Scenarios which reduction in immunosuppression are considered, n (%)[a]	
Persistent BK viruria without viremia	11 (9.7)
Persistent BK viremia without graft dysfunction	76 (67.3)
Persistent BK viremia with allograft dysfunction	81 (71.7)
Presence of biopsy-proven BKVAN	85 (75.2)
Reduction in immunosuppression in the presence of viremia, n (%)[a]	
Reduction in tacrolimus and MMF dose	76 (67.2)
Change to an alternative CNI and antimetabolites	37 (32.7)
Change from CNI to mTORIs	14 (12.4)
Change to low-dose CNI and mTORIs	20 (17.7)
Change from MMF to leflunomide only	30 (26.5)
Use of adjuvant treatment options when BKVAN was diagnosed, n (%)	
Quinolones	
Practice routinely	5 (4.4)
Consider only in some patients	27 (23.9)
Do not use	61 (54.0)
No response	20 (17.7)
Cidofovir	
Practice routinely	11 (9.7)
Consider only in some patients	38 (33.6)
Do not use	44 (38.9)
No response	20 (17.7)
i.v.Ig	
Practice routinely	16 (14.1)
Consider only in some patients	55 (48.7)
Do not use	22 (19.5)
No response	20 (17.7)

Table 2. (Continued)

Trial participation, n (%)	
Yes	77 (68.1)
No	14 (12.4)
No response	22 (19.5)

BKVAN, BK viral associated nephropathy; CNI, calcineurin inhibitors; MMF, mycophenolate mofetil; mTORIs, mammalian target of rapamycin inhibitors
[a]Not mutually exclusive.

and i.v.Ig were considered in some patients and most did not recommend the use of quinolones. Most nephrologists (68%) agreed they would participate in a multicenter intervention trial of BK infection in kidney transplant recipients.

DISCUSSION

This binational survey suggests that BK viral infection is an important early posttransplant complication in kidney transplant recipients. The reported incidence of BK viremia and BKVAN appear to be consistent across Australia and New Zealand, varying between 10% and 15% for viremia and up to 3% for BKVAN. Routine BK polymerase chain reaction testing is the most common screening modality used, but inconsistencies exist between the reported screening frequencies and the international recommended guidelines.[4] In most circumstances, persistent viremia with an elevation in serum creatinine would prompt a diagnostic biopsy to detect BKVAN and exclude other or concurrent causes of allograft dysfunction. Although modification of immunosuppression is universal for all participating units, there is considerable variability in the approaches used to achieve this. More than two-thirds of the nephrologists would reduce the doses of immunosuppressive drugs in the presence of BK viremia or BKVAN, and although there is a wide variation in the immunosuppression reduction strategy, reduction in the total dose of tacrolimus and MMF remains the most favored approach. Adjuvant treatments are not routinely used by the respondents in the treatment of BKVAN, but 43% and 63% would consider prescribing cidofovir and i.v.Ig, , respectively, when other options have failed, or graft function is deteriorating rapidly.

BKVAN remains an important cause of allograft failure in kidney transplant recipients. Despite the high prevalence of BK viremia and the established association between BK viremia and development of BKVAN, the lack of clinical evidence to guide management is likely responsible for the variety of management strategies used, as reported in this survey. Reducing immunosuppression remains the mainstay treatment for BK viremia and BKVAN, but the optimal

approach to reducing or substituting immunosuppressive agents remains uncertain. In this survey, knowledge of the incidence of BK infection and the variability between sites will inform the design of a health care–embedded platform trial. More importantly, we have collected the information to conduct a process of research prioritization, in consultation with consumer groups, to define platform objectives that evaluate key intervention strategies and treatment arms that are currently preferred and commonly used by nephrologists. As most respondents to this survey supported the conduct of a randomized controlled trial to address this research question, a collaborative multicenter clinical study in Australia and New Zealand with a pragmatic trial design is a unique opportunity to address some of these evidence gaps and to inform future clinical management of recipients with BK viremia or BKVAN.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)
Supplementary Methods.
BK Questionnaire.

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Contraceptive Use and Elective Terminations in Women Enrolled in the Glomerular Disease Collaborative Network

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In the United States, nearly half of pregnancies are unintended,[1] and unintended pregnancy is associated with preterm birth and low birth weight.[2] Glomerular disease and vasculitis increase risk of adverse obstetric outcomes including preeclampsia, preterm delivery, and perinatal death.[3] Preventing unintended pregnancy in this high-risk group is imperative, and requires proactive family planning