Screening for BK Viremia Reduces But Does Not Eliminate the Risk of BK Nephropathy: A Single-Center Retrospective Analysis

Richard J. Knight,[1,4] Lillian W. Gaber,[2] Samir J. Patel,[3] Jennifer M. DeVos,[3] Linda W. Moore,[1] and A. Osama Gaber[1]

Background. This study reviewed the outcomes of a screening protocol for BK viremia to determine if early diagnosis, followed by immunosuppression minimization, would prevent progression to nephropathy and graft loss.
Methods. This review included 369 renal transplant recipients tested for BK virus at serial time points after transplantation. Management included immunosuppression minimization plus cidofovir treatment for BK nephropathy.
Results. Recipients received tacrolimus-based immunosuppression, with 8% prednisone-free and 6% who received desensitization. With a mean follow-up of 22±10 months, 16% (n=57) of recipients became BK viremia positive. The median (range) time to diagnosis was 3 (1–17) months. Because renal biopsy was performed selectively, 59% of recipients underwent biopsy, with 47% showing BK nephropathy. Seventy-four percent of recipients cleared the virus at a median (range) time of 9 (3–33) months, with four grafts lost to BK nephropathy. Cidofovir-treated recipients displayed a higher viral load at diagnosis but showed equivalent renal function at last evaluation. In multivariate analysis, recipient age, Asian ethnicity, deceased donor, and prednisone use were factors independently associated with BK viremia. Actuarial survival of BK-positive grafts was worse than that of BK-negative grafts ($P<0.01$, log-rank test). At 9 and 12 months, the mean estimated glomerular filtration rate of the BK-positive group was lower than that of the BK-negative cohort ($P=0.02$).
Conclusions. Despite using a screening protocol combined with immunosuppression minimization, BK-positive recipients had a greater risk of graft loss and impaired function than recipients free of infection. Future investigations should focus on practices to prevent BK viremia.

Keywords: BK viremia, Renal transplantation, Immunosuppression.

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BK nephropathy is an important cause of graft loss after renal transplantation. The emergence of this opportunistic infection coincided with a reduction in the incidence of acute rejection after renal transplantation, suggesting an association with increased immunosuppression. In this regard, it has been shown that the risk of BK virus nephropathy is higher in recipients of antithymocyte globulin and tacrolimus/mycophenolate immunosuppression, the use of prednisone maintenance therapy versus prednisone-free immunosuppression, high versus low trough levels of tacrolimus, and high versus low doses of prednisone (*1–4*). Additional risk factors included African-American recipient ethnicity, deceased-donor transplant recipient status, male recipient gender, a higher degree of HLA mismatch, and a higher number of acute rejection episodes (*5, 6*).

Because there is no effective agent for treatment of BK infection, reduction of immunosuppression is currently the standard of care. Initial studies describing BK nephropathy noted a 50% graft failure rate within 2 years of diagnosis, yet more recent reports have advocated for early diagnosis by screening for BK viuria and viremia. This approach has allowed for early reduction of immunosuppression before significant graft injury, resulting in improved graft outcomes (*7, 8*).

The aim of this single-center study was to review the outcomes of a prospective screening protocol for BK viremia to determine if early diagnosis, followed by a reduction in maintenance immunosuppression, would prevent progression to BK nephropathy and improve outcomes compared with historical data.

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[1] Department of Surgery, The Methodist Hospital, Houston, TX.
[2] Department of Pathology, The Methodist Hospital, Houston, TX.
[3] Department of Pharmacy, The Methodist Hospital, Houston, TX.
[4] Address correspondence to: Richard J. Knight, M.D., Department of Surgery, The Methodist Hospital, 6550 Fannin Street, SM 1661A, Houston, TX 77030.
E-mail: rjknight@tmhs.org
R.J.K. participated in the research design, writing of the article, performance of the research, and data analysis. L.W.G. participated in the writing of the article. S.J.P., J.M.D., L.W.M., and A.O.G. participated in the writing of the article and data analysis.
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RESULTS

Of 369 consecutive renal transplants performed during the study period, 20 subjects were not included in this analysis. Eleven recipients were lost to follow-up, 5 grafts failed, and 4 recipients died, all within the first 3 months after transplantation. None of the excluded transplant recipients were BK viremia positive. Donor and recipient demographics for the remaining 349 patients are shown in Table 1.

The mean follow-up after transplantation was 22±10 months. Fifty-seven (16%) recipients became BK viremia positive during this period. Fifty-four (95%) recipients were diagnosed with BK viremia by routine screening and 3 recipients were at workup for acute renal allograft dysfunction. The median (range) time to diagnosis was 3 (1–17) months (Fig. 1A).

BK Viremia

As shown in Figure 1B, viral load at first diagnosis of BK viremia was relatively low, with 43 (75%) recipients expressing less than 100,000 viral copies/mL. Thirty-two of 54 (59%) recipients underwent renal biopsy after diagnosis of BK viremia, with 15 (47%) biopsies positive for BK infection. All positive biopsies were associated with BK viremia. Seven biopsies were graded as pattern A and eight were graded as pattern B based on the degree of tubulointerstitial infiltrate and fibrosis.

The mean viral load of recipients with a positive biopsy was 545,650±750,178 versus 86,833±175,345 copies/mL (P=0.017) for recipients with a biopsy negative for BK infection. Yet, of those recipients who underwent renal biopsy, 47% with an initial viral load more than 100,000 copies/mL had a positive biopsy for BK virus, as did 47% recipients with an initial viral load of less than 100,000 copies/mL (P=nonsignificant).

TABLE 1. Donor and recipient demographics (n=349)

Donor age, yr, mean±SD	39±15
Deceased donors, n (%)	194 (56)
Extended criteria deceased donors, n (%)	33 (9)
Cold ischemia time, hr, mean±SD	20±8
Recipient age, yr, mean±SD	48±14
Male recipients, n (%)	195 (56)
Recipient ethnicity, n (%)	
Caucasian	161 (46)
African American	94 (27)
Hispanic	72 (21)
Asian	22 (6)
Desensitization treatment, n (%)	22 (6)
Initial graft function, n (%)	
Immediate	250 (72)
Slow[a]	66 (19)
Delayed	33 (9)
Acute rejection, n (%)	36 (10)

[a] Slow graft function defined as less than 30% decline in serum creatinine from posttransplantation days 1 to 2 without the need for dialysis in the first week after transplantation.

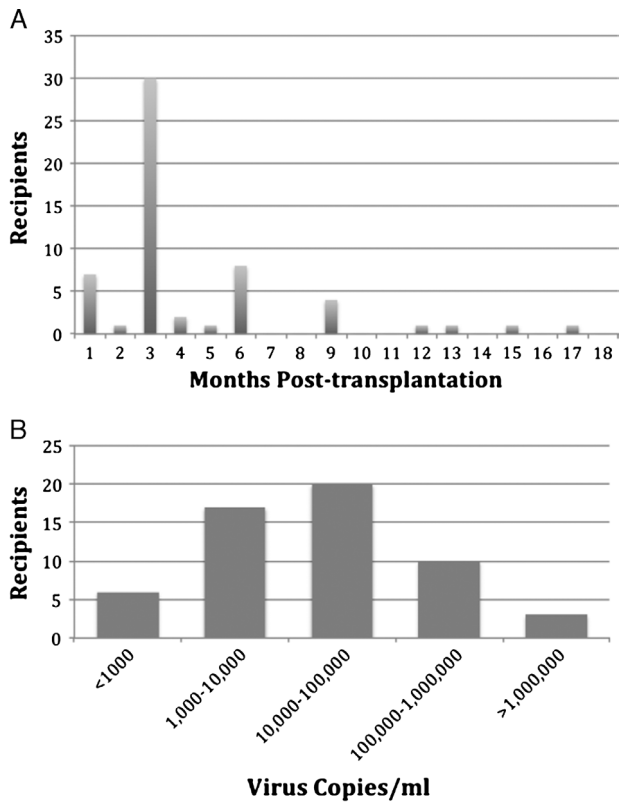

FIGURE 1. A, median (range) time to initial diagnosis of BK viremia was 3 (1–17) months. B, viral load at first diagnosis of BK viremia.

At most recent follow-up, 40 of 57 (74%) recipients have cleared the virus, with a median (range) time to viral clearance of 9 (3–33) months.

Eighty-seven percent of BK-positive recipients with an early response to treatment, as measured by a decline in viremia within the first 3 months of diagnosis, ultimately cleared the virus, whereas, among recipients who showed an increase in viral copies at 3 months, only 44% had cleared the virus at last follow-up (P=0.08). Among the latter group, there was no relationship between the rate of increase in viral copies and viral clearance.

Three of 57 (5%) patients suffered a biopsy-proven acute rejection within 3 months of the diagnosis of BK infection, suggesting that the rejections may have been associated with a reduction in immunosuppression. Two other patients suffered acute rejections that progressed to graft loss. In both cases, the rejection episodes occurred more than 2 years after the diagnosis of BK viremia. In the first case, the rejection episode was related to noncompliance with immunosuppression medication. In the second case, the acute rejection was related to low tacrolimus levels associated with the introduction of an antiseizure medication.

Cidofovir Treatment

In addition to immunosuppression reduction, 33 of 57 (58%) BK-positive recipients received treatment with cidofovir. Indications for treatment included an initial viral

TABLE 2. Outcomes of cidofovir-treated and untreated recipients with BK viremia

	Cidofovir treated (n=33)	Untreated (n=24)	*P*
Initial viral load, copies/mL, mean±SD	271,665±470,447	42,918±106,235	0.023
Follow-up, mo, mean±SD	22±10	21±8	NS
eGFR, mL/min, mean±SD	54.8±22.3	61.5±22.1	NS

eGFR, estimated glomerular filtration rate; NS, nonsignificant.

load more than 100,000 copies and a biopsy showing evidence of BK nephropathy. As shown in Table 2, this cohort had a higher initial viral load than the untreated group but, with similar follow-up time, showed equivalent renal function at last evaluation. All four recipients who lost grafts to BK nephropathy were treated with cidofovir. Treatment was continued for 6 months or until viral clearance. Cidofovir was well tolerated with no reported adverse events.

Graft Losses

Seven recipients suffered graft losses. Four losses were directly associated with BK infection, one loss was due to patient death, and two losses were due to acute rejection, unrelated to BK viremia. Thus, with a median follow-up of 20 months for the 57 recipients who became BK viremia positive, the risk of graft loss related to BK nephropathy was 7%.

Of the four grafts that were ultimately lost to BK nephropathy, one was first diagnosed on workup of acute renal dysfunction. Prior screenings for BK viremia had been negative. Yet, at the time of biopsy, the recipient was BK viremia positive. The initial viral load for this recipient was less than 100,000 copies/mL. The other three grafts lost to BK were first diagnosed on routine screening with normal renal function. The initial viral load was more than 100,000 copies/mL for all three graft recipients, whereas, as previously noted, 75% of recipients were initially diagnosed with a viral load less than 100,000 copies/mL. Additionally, all three grafts were biopsied at the initial finding of BK viremia and showed evidence of BK infection. Thus, 3 of 14 (21%) grafts with an initial viral load of more than 100,000 copies/mL proceeded to graft loss due to BK infection versus only 1 of 43 (2%) grafts with an initial viral load of less than 100,00 copies/mL (P=0.04).

Risk Factors for BK Viremia

Characteristics of recipients who became BK viremia positive during the follow-up period were compared with recipients who remained BK negative, as shown in Table 3. In univariate analysis, older recipient age, Asian ethnicity, receipt of a deceased donor graft, and the use of prednisone were associated with BK viremia. Recipient gender, donor age, initial graft function, the use of thymoglobulin induction, and an early acute rejection episode were not significantly related to BK viremia. Mean follow-up times were equivalent between groups. In multivariate analysis, recipient age greater than 60 years, Asian ethnicity, recipients of deceased donors, and the use of prednisone were all factors that remained independently associated with BK viremia (Table 4).

TABLE 3. Univariate analysis of risk factors for BK viremia

	BK viremia positive (n=57)	BK viremia negative (n=292)	*P*
Recipient age >60 yr, n (%)	19 (33)	38 (13)	0.02
Male gender, n (%)	35 (61)	160 (55)	NS
Ethnicity, n (%)			
Caucasian	22 (38)	139 (48)	NS
African American	16 (28)	78 (27)	NS
Hispanic	10 (18)	62 (21)	NS
Asian	9 (16)	13 (4)	0.01
Deceased donor, n (%)	41 (72)	155 (53)	0.01
Donor age, yr, mean±SD	37±13	40±15	NS
Initial graft function, n (%)			
Immediate	39 (68)	211 (72)	NS
Slow	11 (19)	55 (19)	NS
Delayed	7 (12)	26 (9)	NS
Desensitization treatment, n (%)	5 (9)	17 (6)	NS
Thymoglobulin induction, n (%)	38 (67)	185 (63)	NS
Prednisone free, n (%)	1 (2)	28 (10)	0.05
Early acute rejection[a], n (%)	1 (2)	16 (6)	NS
Follow-up time, mo, mean±SD	23±8	22±8	NS

[a] Biopsy-proven acute rejection within first 3 months after transplantation.
NS, nonsignificant.

TABLE 4. Multivariate analysis of risk factors for BK viremia

	Odds ratio	95% Confidence interval	*P*
Age >60 yr	1.92	0.99–3.64	0.05
Asian ethnicity	4.36	1.6–11.89	0.005
Deceased donor	1.96	1.05–3.81	0.03
Prednisone free	0.14	0.007–0.75	0.02

Graft Survival

Of grafts with function at 3 months after transplantation, actuarial survival of BK-positive grafts was significantly worse than that of BK-negative grafts ($P<0.01$, log-rank test), as shown in Figure 2. As noted above, there were seven graft losses in the BK-positive cohort. Four losses were related to BK infection, one loss was due to patient death, and two losses were due to acute rejection, unrelated to BK viremia. There were nine graft losses in the BK-negative cohort. Six losses were due to patient death, two losses were due to chronic rejection, and one loss was due to acute rejection resulting from medication noncompliance.

Renal Function

The mean estimated glomerular filtration rates (eGFR; Modification of Diet in Renal Disease study equation) of the BK viremia–positive and BK viremia–negative cohorts at 1, 3, 6, 9, and 12 months after transplantation are shown in Figure 3. At both 9 and 12 months after transplantation, the mean eGFR of the BK-positive group was lower than that of the BK-negative cohort ($P=0.02$). Additionally, 12 of 57 (21%) BK-positive grafts suffered marked (>25%) decline in eGFR from month 3 to the most recent follow-up compared with only 31 of 292 (11%; $P=0.049$) of BK-negative grafts over a similar period of time.

DISCUSSION

The principle finding of our study, in contradistinction to a number of recent reports of BK screening (*8, 9*), was that diagnosis of BK viremia, before clinical evidence of renal dysfunction, did not eliminate the risk of graft loss or dysfunction associated with BK nephropathy. In fact, once diagnosed with BK viremia, the risk of graft loss was increased and the quality of graft function was reduced compared with grafts of recipients free of BK viremia. Nevertheless, early diagnosis likely prevented many kidneys from progressing to BK nephropathy and graft loss. Certainly, the results suggest a better outcome compared with reports published before the era of prospective screening for BK viremia and viuria (*7*).

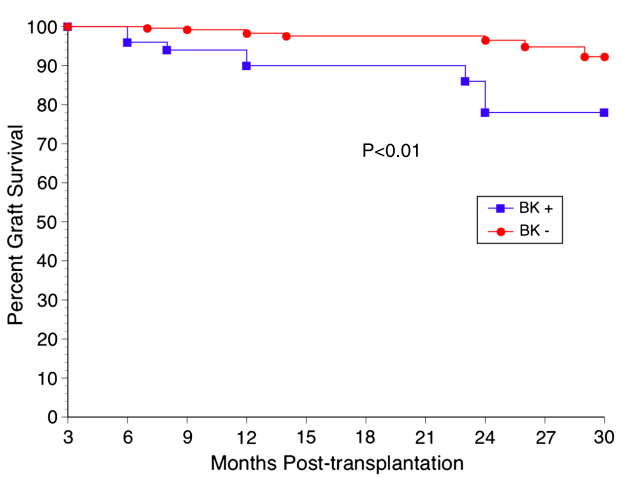

FIGURE 2. Kaplan–Meier plot comparing survivals of BK-positive and BK-negative renal allografts with function at 3 months after transplantation ($P<0.01$, log-rank test).

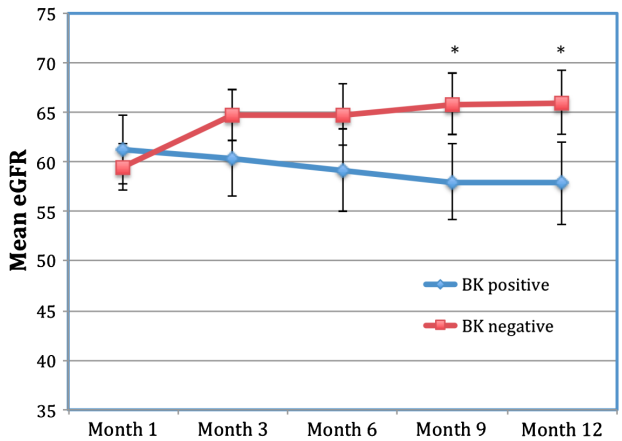

FIGURE 3. Mean±SEM eGFR of BK viremia–positive and BK viremia–negative cohorts at selected time points after transplantation. *At months 9 and 12, mean eGFR of the BK-positive group was significantly lower than that of the negative cohort ($P=0.02$). eGFR, estimated glomerular filtration rate.

This report of 349 renal allograft recipients prospectively screened for BK viremia is among the largest studies presented to date. The incidence of BK viremia was 16%, comparable with other studies, and management by reduction in immunosuppression was consistent with current recommendations (*10*). The benefit of cidofovir remains unclear, because all recipients, in addition, had immunosuppression reduced. Most recipients were diagnosed early after transplantation, typically at 3 months, with a relatively low level of BK viremia and with renal function unchanged from baseline. Almost 50% of biopsies showed evidence of BK nephropathy and all positive biopsies were graded as showing mild to moderate degree of cellular infiltrate or fibrosis. There was an uncertain correlation between initial viral load and the presence of BK infection on biopsy. The mean viral load of recipients with a positive biopsy was significantly higher than that of recipients with negative biopsies. However, recipients with an initial viral load less than 100,000 copies/mL were equally likely to have a positive biopsy as recipients with initial viral loads more than 100,000 copies/mL. Risk of graft loss due to BK nephropathy was correlated with an initial viral load more than 100,000 copies/mL. Clearance of virus was more likely in recipients showing an early decline in viral counts.

Demographics of BK-positive and BK-negative recipients were generally similar, although, consistent with other

published reports, older recipient age, receipt of a deceased donor, and the use of prednisone were all factors independently associated with BK viremia. Interestingly, in this study, we also found that Asian recipients were more likely to become BK viremia positive. Of importance, the actuarial graft survival of BK viremia–positive recipients was worse than that of the BK-negative cohort. Moreover, despite appropriate management, 4 of 57 such grafts were lost to causes related to BK nephropathy.

Although early graft function was similar between groups, by 9 months after transplantation, the mean eGFR of affected grafts was inferior to that of unaffected kidneys. Additionally, compared with BK-negative kidneys, a larger percentage of BK-positive grafts had suffered a decline in renal function at last follow-up. This reduction in renal reserve among the successfully treated cohort is likely a consequence of renal injury due to BK nephropathy. Because renal function at 1 year after transplantation has been correlated with long-term graft survival, it would suggest that, with longer follow-up, this group might suffer even more graft attrition compared with the unaffected cohort.

As with all retrospective single-center reviews, there are a number of limitations to this study. Although all recipients received a tacrolimus/mycophenolate-based immunosuppression protocol, 8% of recipients were prednisone-free and 6% of recipients received desensitization therapy before transplantation. Additionally, only 57% of recipients underwent renal biopsy after diagnosis of BK viremia. The use of cidofovir was, in part, based on the finding of BK nephropathy; thus, the treatment protocol was, to a degree, inconsistent.

As mentioned, the results herein are at odds with recent published reports describing superior outcomes using similar prospective screening protocols followed by immunosuppression minimization. In this regard, a publication by Schaub et al. describes a similar prospective screening protocol followed by reduction in immunosuppression. In their study of 203 patients, they found a 19% incidence of BK viremia, with 92% clearance of virus at last follow-up. There were no graft losses to BK nephropathy and a remarkable 100% death-censored graft survival at 3 years. In that study, monitoring was performed more frequently in the early posttransplantation period compared with our protocol, yet both the incidence of BK viremia and the immunosuppression reduction regimen were very similar to our report (*9*).

Similarly, Brennan et al. prospectively monitored 200 renal allografts recipients and described an 11% incidence of BK viremia. In that study, immunosuppression reduction consisted of complete withdrawal of the antimetabolite followed by reduction in the dose of calcineurin inhibitor as needed. They reported no graft losses to BK nephropathy and no impairment in renal function (*8*).

Similar to our own findings, a number of smaller single-center studies have recorded graft losses and impaired renal function despite the institution of screening protocols accompanied by immunosuppression reduction for BK viremia (*7, 11, 12*). Specifically, Vasudev et al. (*13*) reported a 36% graft loss due to BK nephropathy despite instituting screening for BK viremia followed by immunosuppression reduction.

Our data should thus raise a note of caution regarding the current optimism in the management of BK viremia and nephropathy. As a treatment algorithm, screening accompanied by immunosuppression reduction has resulted in improved outcomes but is not a panacea. We have followed currently recommended guidelines for the management of BK viremia but have not achieved the excellent published results described above. Arguably, results would have been improved with more frequent monitoring, yet the protocol outlined herein of testing at months 1, 3, 6, 9, and 12 and every 6 months is consistent with published Kidney Disease: Improving Global Outcomes guidelines. That protocol recommends screening for months 1 to 3 and then every 3 months until 1 year after transplantation (*10*).

Thus, in our view, the current treatment paradigm of viral monitoring followed by immunosuppression reduction does not appear adequate to manage what has become the most common viral infection in renal transplant recipients. Moreover, one must also take into account the enormous workload placed on a busy transplant program to effectively monitor all transplant recipients for BK viremia and appropriately manage immunosuppression reduction in affected recipients. Thus, it seems reasonable to focus on addressing possible modifiable risk factors, such as novel immunosuppression/antibiotic protocols to prevent the emergence of BK viremia. Based on data presented herein, and the work of others (*1, 2*), it could be recommended that a prednisone-free maintenance immunosuppression regimen would lower the risk of BK viremia. Similarly, there are data suggesting that both sirolimus and fluoroquinolones may prevent BK virus replication (*14, 15*). These are all interventions that should be explored to reduce the incidence of BK viremia.

In summary, a prospective screening protocol combined with immunosuppression reduction recorded improved outcomes for renal transplant recipients diagnosed with BK viremia compared with historical data. Nonetheless, BK-positive recipients had a greater risk of graft loss and, at 1 year after transplantation, impaired function compared with recipients free of infection. Future investigations should focus on more innovative practices to prevent BK viremia.

MATERIALS AND METHODS

Study Population

This retrospective review of a single-center experience included 369 consecutive renal transplant recipients performed between August 2007 and July 2010. All subjects included in this review received a kidney-alone transplant and were followed for at least 3 months or until graft loss.

Immunosuppression

Subjects considered at high risk of acute rejection (African Americans, retransplantation, and highly sensitized recipients) received a 3-day course of rabbit antithymocyte globulin (thymoglobulin; Genzyme, Cambridge, MA) at a dose of 1.5 mg/kg per day beginning on the day of transplantation. All other subjects received 2.0 mg/kg daclizumab (Zenapax; Roche, Nutley, NJ) on the day of transplantation and on posttransplantation day 3. Maintenance immunosuppression consisted of tacrolimus, mycophenolate mofetil, and prednisone. The dose of tacrolimus was adjusted to maintain a trough level of 8 to 10 ng/mL for the first 3 months after transplantation, tapered to 5 to 8 ng/mL thereafter. Mycophenolate mofetil was given at a dose of 1000 mg twice daily. Methylprednisolone (250 mg) was given on the

day of transplantation, tapered to 25 mg by day 5 and then to 5 to 10 mg by 6 months after transplantation. By physician preference, a small number of patients were withdrawn from prednisone on posttransplantation day 6. This cohort was restricted to non–African-American recipients receiving a first transplant with a panel reactive antibody less than 20%. The protocol required thymoglobulin induction with complete steroid withdrawal at day 5 after transplantation. Additionally, a small group of living-donor recipients with pretransplantation donor-specific antibody received desensitization therapy that included intravenous immunoglobulin, rituximab, and plasmapheresis.

BK Viremia Testing

All recipients were tested for BK virus by serum polymerase chain reaction at months 1, 3, 6, 9, 12, 18, and 24 after transplantation. Additionally, BK viremia testing was performed for an unexplained rise in serum creatinine. A positive diagnosis of BK viremia required two tests showing more than 750 viral copies/mL. After diagnosis of BK viremia, recipients were tested on a monthly basis until disappearance of viremia. Viral clearance was defined as two consecutive monthly tests showing less than 750 viral copies/mL.

BK Nephropathy

Most subjects who tested positive for BK viremia underwent renal biopsy to assess for evidence of BK nephropathy. At the introduction of the screening protocol, renal biopsy was performed selectively based on the individual preference of the treating physician. Because the biopsy data were reviewed, it became apparent that a large percentage of biopsies were positive for BK nephropathy. The protocol was then modified so that all patients with BK viremia underwent biopsy. Additionally, all recipients with an unexplained rise in serum creatinine underwent renal biopsy. Confirmation of BK nephropathy was performed using an immunoperoxidase stain for the simian virus 40 large T antigen. Nephropathy was graded as pattern A, B, or C based on the degree of tubulointerstitial inflammatory infiltrates and fibrosis (*16*).

Management of BK Viremia

Treatment of BK viremia consisted of concurrent reduction in the dosages of both tacrolimus and mycophenolate mofetil. The tacrolimus dose was targeted to a trough level of 4 to 6 ng/mL and the dosage of mycophenolate mofetil was reduced by 50%. Additionally, cidofovir was given every 2 weeks at a dosage of 0.5 mg/kg for recipients with either a high initial viral load or evidence of BK nephropathy on biopsy. Cidofovir treatment continued until clearance of virus but not longer than 6 months.

Statistical Analysis

Statistical analyses were performed using JMP 9 (SAS Institute, Cary, NC). Recipient characteristics were categorized and compared using chi-square test or Fisher's exact test to determine an association with BK development, with $P<0.05$ representing statistical significance. All factors found to approach significance ($P<0.1$) by univariate analysis were included in a nominal logistic fit model to determine independent risk factors associated with BK viremia. Graft survival was depicted using Kaplan–Meier curves and calculated using the log-rank test.

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