**High dose intravenous immunoglobulin treatment for the prevention of BK virus nephropathy in pediatric renal transplant recipients**

**Abstract**

**Background:** BK virus nephropathy (BKVN) is diagnosed in 5%–16% of pediatric renal transplant recipients and is preceded by BK-viruria and BK-viremia. Despite the risk of irreversible kidney damage associated with BKVN, there is a lack of evidence-based guidelines for preventing BKVN in patients with BK-viruria/viremia.

**Aims:** In this retrospective study, we examined the safety and efficacy of high-dose intravenous immunoglobulin (HD-IVIG) therapy in the prevention of BKVN in pediatric renal transplant recipients with BK-viruria/viremia.

**Methods:** All pediatric renal transplant recipients under our care underwent routine testing for BK virus in urine and blood, using the polymerase chain reaction (PCR) technique. Patients with BK-viruria of up to 107 copies/mL and/or BK-viremia of up to 103 copies/mL, and without evidence of active BKVN, were treated with a 50% dose reduction of the immunosuppressive drug mycophenolate mofetil (MMF). Patients who had no decline in BK viral load within two months of MMF dose reduction were treated with HD-IVIG at 2 g/kg body weight.

**Results:** The study included 62 patients over a six-year follow-up period. Thirty-one patients (50%) demonstrated BK-viruria/viremia. Thirteen of the patients (42%), who had a high viral load that was unresponsive to MMF dose reduction, were treated with HD-IVIG. In 12 of the 13 patients (92%) treated with HD-IVIG, the viral load was substantially reduced, and viral clearance was achieved within six months from the completion of HD-IVIG therapy. One patient (8%) experienced an increase in viral load despite HD-IVIG therapy. Except for transient headaches, there were no major adverse effects of HD-IVIG treatment in any of the patients. None of the patients developed BKVN during the study period.

**Conclusions:** Preventive HD-IVIG therapy in pediatric renal transplant recipients with BK- viruria/viremia unresponsive to MMF dose reduction is safe and effective in preventing the development of BKVN. Additional studies are required to establish our findings further.

**Introduction**

The BK virus (BKV) belongs to the family of polyomaviruses, which are nonenveloped, double-stranded DNA viruses that are disease-causing in immunocompromised patients. The BKV was initially isolated from the urine of a renal transplant recipient and is named after the patient’s initials. A latent form of BKV tends to be present in kidney tissue and the urinary system. While most BKV infections in healthy people are asymptomatic, immunocompromised patients and recipients of kidney or bone marrow transplants can develop a severe symptomatic disease [1].

BKV nephropathy (BKVN) is a severe complication of BKV infection in renal transplant recipients that can lead to graft loss. Although 30%–40% of adult renal transplant recipients develop BK-viruria following transplantation, and 10%–30% develop BK-viremia, BKVN occurs only in 5%–8% of all recipients. However, in a high proportion (80%–90%) of patients with BKVN, the damage to the graft is irreversible and can lead to graft loss within five years from diagnosis [2, 3]. Therefore, it is critical to monitor the viral load of BKV in renal transplant recipients and to use early intervention in patients who are at a high risk of developing BKVN.

Primary BKV infections mainly occur during childhood through exposure to respiratory secretions or urine of carriers. In immunocompetent hosts, the infection is usually asymptomatic or experienced as a mild upper respiratory tract infection. The virus spreads through the bloodstream to other organs and remains largely inactive in kidney cells and the urinary system. Serologic evidence for a prior BKV infection can be found in 90% of the adult population.

BKVN in adult renal transplant recipients develops from viral reactivation in the urinary tract, whereas pediatric recipients mostly undergo primary BKV infections by virus acquired from the donor at the time of transplantation. BKV reactivation in renal transplant recipients begins with increased viral replication in the graft tissue followed by viral shedding in the urine. BK-viruria precedes BK-viremia, and BKVN develops subsequently to BK-viremia. The reported time interval between BK-viruria and BK-viremia is one to three months [2].

Most pediatric renal transplant recipients had not been previously exposed to BKV. They lack natural immunity to the virus and are at a high risk of undergoing primary BKV infections at the time of transplantation. Approximately 50% of pediatric renal transplant recipients develop BK-viruria/viremia during the first year post-transplantation [4]. However, only a small number of studies compared the epidemiology and risk of BKVN between children and adults, and there are no standardized guidelines for the diagnosis, prevention, and treatment of BKV infections in pediatric renal transplant recipients [4, 5].

Most cases of infection or reactivation of latent BKV occur in the first months post-transplantation, while patients receive the highest doses of medications that suppress graft rejection and immunosuppressive therapy. The placement of ureteral double-J stents is another risk factor for accelerated viral replication and development of BKVN [6]. Additional risk factors for developing BKVN in renal transplant recipients include male sex, pediatric patient, deceased donor, congenital anomalies of the urinary tract, delayed initial graft function, and a tacrolimus-based regimen [4, 7].

The clinical diagnosis of BKVN can be challenging because it usually presents as an asymptomatic decline in renal function and requires confirmation by a renal biopsy [8]. The typical histological findings in BKVN result from tubular damage and present as tubulointerstitial nephritis with inflammatory lymphocytic infiltrate that can be mistaken for acute graft rejection, tubular atrophy, and interstitial fibrosis. Pathognomonic histological findings of BKVN include the presence of BKV intranuclear inclusion bodies and positive immunohistochemical staining of simian virus 40 (SV-40) large T-antigen. The level of inflammation and interstitial fibrosis are positively related to disease severity and the risk of graft loss [3].

Monitoring BKV viral load is of critical importance because of the association between viral load and the risk of BKVN. Viral copy number in urine and blood is determined by real-time polymerase chain reaction (RT-PCR). A viral load of over 107 copies/mL in the urine or over 103 copies/mL in the blood, measured for over three weeks, is considered a laboratory marker for a high probability of BKVN. However, kidney biopsy remains the gold standard for diagnosis of BKVN and is used to inform the choice of treatment options [9]. BKV blood level monitoring is a routine practice in most transplantation centers, whereas the need to monitor viral load in the urine is controversial and is not performed routinely in all centers.

Because the accelerated replication of BKV in renal transplant recipients results from immunosuppression, reducing the doses of immunosuppressive medications is a preventative and first-line treatment approach in patients with a high viral load or proven nephropathy. However, there are no standardized guidelines for reducing immunosuppressive treatment in renal transplant recipients with a high viral load or BKVN [5]. Different protocols have been suggested, including a switch from tacrolimus to cyclosporine, dose reduction of mycophenolate mofetil (MMF), a switch from calcineurin blockers to mTOR inhibitors, and others. However, reports of the efficacy of these protocols are contradictory. Reducing immunosuppressive therapy can lead to acute graft rejection and requires vigilant monitoring of renal function [10]. Adjunct therapies with limited efficacy in renal transplant recipients with a high viral load of BKV include leflunomide, an anti-inflammatory drug with anti-viral and immunosuppressive properties [11], and quinolones [12]. Cidofovir is recommended for patients who do not respond to these adjunct therapies. Cidofovir, a nucleoside analog active against cytomegalovirus (CMV), is also effective in BKV treatment. However, cidofovir is nephrotoxic and should be used cautiously in renal transplant recipients [13].

Immunoglobulins, commercially extracted from many blood donors, contain a mix of neutralizing antibodies against different strains of BKV [1]. Evidence from case reports, small case series, and uncontrolled clinical studies suggest that HD-IVIG effectively reduces BKV viral load in adult patients who had not responded to dose-reduction of immunosuppressive therapy [14–16]. Given that a high proportion of pediatric recipients are BKV-naïve prior to renal transplantation [4], the efficacy of HD-IVIG treatment in reducing BKV viral load in children warrants examination.

**Aims**

The study aims to determine the demographic and clinical characteristics in pediatric renal transplant recipients with BK-viruria/viremia who are under the care of a tertiary medical center in northern Israel; to identify risk factors for the development of a high viral load, and to examine the safety and efficacy of HD-IVIG treatment in reducing the viral load and preventing the development of BKVN.

**Patients and methods**

This retrospective study included all pediatric renal transplant recipients who were 20 years old or younger at the time of transplantation and were under the care of the Pediatric Nephrology Institute at the Rambam Medical Center between January 2014 and December 2019. Internal ureteric double-J stents were retained in all patients for three to six weeks post-surgery. All patients received induction therapy with high doses of the steroids basiliximab or thymoglobulin, and maintenance therapy with steroids, MMF, and tacrolimus. BKV viral load in urine and blood was determined by PCR immediately after surgery, once every two weeks during the following three months, and once every one to three months after that, according to clinical considerations. BK-viruria of up to 107 copies/mL without evidence for BK-viremia was monitored without intervention. BK-viruria of up to 107 copies/mL together with BK-viremia of up to 103 copies/mL was treated by a 50% dose-reduction of MMF with supplementation of quinolines. We chose to reduce the MMF dose because of the increased risk for graft rejection with dose reduction of tacrolimus [17]. Patients with further increase in viral load or without reduction in BK-viruria of at least two orders of magnitude and /or persistent BK-viremia for two months after the dose reduction of MMF and quinoline supplementation, were treated with HD-IVIG at a total dose of 2g/kg body weight. The HD-IVIG preparations were aliquoted into two to five equal doses that were administered on consecutive days. The Wilcoxon rank-sum test and Z-test were used for statistical analyses of the results.

**Results**

The study included 62 pediatric renal transplant recipients over a six-year follow-up period.

Patients’ age at the time of surgery was 2–20 years (median 13 years). Thirty-seven children received a kidney from a deceased donor and twenty-five from a living donor. Thirty-one patients (50%) had a negative BKV PCR throughout the study period, and the remaining thirty-one patients (50%) had a positive urine BKV PCR after surgery. All patients with BKV became virus-positive during the first year after transplantation, with a median time of five months. Six of the BK-positive patients (10%) had BK-viruria of up to 107 copies/mL that declined or self-resolved without intervention within three months from diagnosis and had no evidence for BK-viremia.

Twenty-five of the BK-positive patients (81%) had increased urinary viral load ranging from 1.5x106 to 1.8x107 copies/mL, and seven of these patients developed BK-viremia with a viral load ranging from 104 to 7.8x104 copies/mL. All 25 patients were treated by MMF dose reduction. In 12 patients, this treatment produced BKV clearance from the blood and substantially reduced the viral load in the urine without further treatment. One patient (4%) developed acute cellular graft rejection that was diagnosed in a renal biopsy. The patient responded well to treatment for suppression of rejection, and the graft remained functional without further BKV infection.

In 13 (52%) of the 25 BKV-positive patients treated with MMF dose reduction, the urinary viral load increased up to 109 copies/mL, and BK-viremia of up to 105copies/mL developed in all patients, although there was no decline in graft function. All 13 patients were treated with HD-IVIG, as detailed above. Two of the patients had unsatisfactory responses to the treatment and required an additional dose of HD-IVIG, which was administered two months after the first dose. In 12 of the patients (92%), BKV clearance was demonstrated within one to five months from the HD-IVIG administration, and none of the patients had a recurrent BKV-viruria/viremia or BKVN during the two to five years of follow-up. One of the 13 patients (8%) had no decline in BKV viral load even after two doses of HD-IVIG and required cidofovir treatment. All patients tolerated the HD-IVIG treatment well, and the only adverse event was a transient headache that responded to oral paracetamol within 24 hours.

As indicated above, in two of the patients, the reduction in viral load was unsatisfactory after the first dose of HD-IVIG, with persistent, ongoing BK-viremia. Diagnostic renal biopsies from the two patients showed no evidence of BKVN, and immunohistochemical staining for SV-40 was negative. The two patients were treated with a second dose of HD-IVIG. In one patient, BKV was cleared from urine and blood within several weeks, and the graft has been functioning well during the five-year follow-up period. The second patient had a sustained BK-viremia of over 104 copies/mL after the second dose of HD-IVIG. Given the high risk of BKVN in this patient, she was treated with cidofovir, which substantially reduced the urinary viral load to a titer of 104–105 copies/mL and cleared the viremia. Despite the ongoing BK-viruria in this patient, the graft has been functioning well during the three-year follow-up period, with no evidence of nephropathy.

Analysis of demographic and clinical characteristics of the patients in our study (Table 1) found that pediatric renal transplant recipients who became BK-positive following transplantation had a younger median age (10 years, compared to 14 years in the BK-negative group). The proportion of girls in the BK-positive group (45%) was slightly higher than their overall proportion in the study group (40%) and their proportion in the BK-negative group (35%). Although these were minor differences that were not statistically significant, girls were overrepresented in the group of patients who had high viral load and required HD-IVIG treatment (8/13, 62%). The proportion of recipients with congenital anomalies of the urinary tract was higher in the group of BKV-positive patients (58%) than their overall proportion (47%) and their proportion in the BKV-negative group (35%). A kidney from a deceased donor was transplanted in 62% of the BK-positive patients and 52% of the BK-negative patients. In the BKV-positive group, only one out of the six patients who had self-resolution of the viral infection received a kidney from a deceased donor. In contrast, 19 of the 25 patients (76%) who had a high viral load that required medical intervention received kidneys from deceased donors. Eleven of the sixty-two patients (18%) required an alternative induction therapy with increased suppression of graft rejection because of immune hypersensitivity or acute graft rejection. Three patients in this group (10%) were BK-negative, whereas the remaining eight patients (26%) had a high viral load of BKV that required HD-IVIG treatment.

**Summary and discussion**

Our study is the first to examine clinical and epidemiological characteristics of BKV infection in a cohort of pediatric renal transplant recipients in Israel. The rate of BK-viruria/viremia in our cohort was 50%, with 20% of the patients demonstrating a very high viral load. These rates are consistent with the literature [4]. Risk factors for BKV-infection in our cohort included a young age at the time of transplantation, congenital anomalies of the urinary tract, a deceased donor, and intense treatment for suppression of graft rejection. Similar risk factors have been reported previously [4, 5, 18]. Although the difference in sex distribution between the BK-positive and BK-negative groups was not statistically significant, females were overrepresented in the group of patients with a very high viral load and a persistent infection.

In contrast to the reported rate of 5%–8% BKVN in pediatric renal transplant recipients, we found no histological evidence for nephropathy in any of the patients in our cohort, including the patient with BK-viremia of >104 copies/mL, which is classified as probable or presumptive BKVN [5]. The absence of BKVN may be related to the relatively small number of patients in our study or to false-negative findings in kidney biopsy. However, we cannot exclude the possibility that the absence of BKVN in our study cohort was related to the close monitoring of BKV viral load in blood and urine and the rapid use of preventative therapy – dose reduction of MMF and administration of HD-IVIG. The protocol used in our study for monitoring BKV viral load was more stringent than suggested in the standardized guidelines, which recommend that viral load be monitored at a lower frequency during the first two months post-transplant and does not generally recommend monitoring BKV titer in the urine [5]. The need for routine monitoring of BKV viral load in the urine is controversial because of the test’s high sensitivity and low specificity in diagnosing nephropathy secondary to BKV infection. According to the standardized guidelines, a high BKV viral load in the urine is not an indication for changing the treatment regimen. However, given the short period between the transplantation and the conversion of most recipients to BKV-positive, and the fact that 50% of patients with BK-viruria subsequently develop BK-viremia, there may be only a short window of opportunity for the use of therapy that produces a rapid decline in viral load in urine and blood and prevents irreversible damage to the grafted kidney.

It is widely agreed that reducing immunosuppressive therapy is effective in lowering BKV viral load and preventing BKVN in pediatric and adult renal transplant recipients, although the reported associated risk for acute graft rejection is 10% in adults [4] and 15% in children [19]. In our study, only one patient in the BKV-positive group (3%) developed acute graft rejection following the dose reduction of MMF. The low incidence of acute graft rejection in our cohort may be related to the small number of patients, the close monitoring of viral load, or HD-IVIG administration. Because HD-IVIG is used routinely to prevent humoral kidney graft rejection, the possibility that this treatment can prevent graft rejection in renal transplant recipients with a high BK-viral load cannot be excluded.

The efficacy of IVIG in renal transplant recipients with a high viral load of BKV had been previously investigated, and results generally indicated a lowering of the viral load. However, it is difficult to draw clear conclusions from the studies because of the great variability in patient characteristics, treatment aims (preventative versus therapeutic), sample size, research methodology, and drug combinations used [14, 20]. In addition, there are only sporadic reports of IVIG use in children [15,16], and the treatment had not been investigated in pediatric renal transplant recipients.

To the best of our knowledge, this is the first study of the efficacy of HD-IVIG as a preventative therapy in a cohort of pediatric renal transplant recipients with a high viral load but without BKVN. The limitations of our study are the relatively small number of patients, the retrospective methodology, and the absence of a control group. Without a control group, we cannot determine what proportion of patients with a high viral load would not develop BKVN, or alternatively, develop graft rejection, without HD-IVIG treatment. We conclude that HD-IVIG is a safe and effective treatment option for the prevention of irreversible kidney damage in pediatric renal transplant recipients with a high viral load. Large, prospective controlled trials are required to further establish the findings of this preliminary study.

Table 1: Clinical and demographic characteristics of pediatric kidney transplant recipients with and without positive PCR for BKV

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| --- | --- | --- | --- | --- |
|  | Total number of recipients (%) | BKV-negative | BKV-positive |  |
| Number of patients | 62 | 31 (50%) | 31 (50%) |  |
| Median age (years) | 13 | 14 | 10.5 |  |
| Female sex | 25 (40%) | 11 (35%) | 14 (45%) | p=0.435 |
| Congenital urinary tract anomalies | 29 (47%) | 11 (35%) | 18 (58%) | p=0.076 |
| Deceased donor | 37 (59%) | 17 (52%) | 20 (62%) | p=0.435 |
| Increased immunosuppressive therapy | 11 (18%) | 3 (10%) | 8 (26%) | p=0.097 |