BK Virus Nephropathy and Kidney Transplantation

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Nephropathy from BK virus (BKV) infection is an evolving challenge in kidney transplant recipients. It is the consequence of modern potent immunosuppression aimed at reducing acute rejection and improving allograft survival. Untreated BKV infections lead to kidney allograft dysfunction or loss. Decreased immunosuppression is the principle treatment but predisposes to acute and chronic rejection. Screening protocols for early detection and prevention of symptomatic BKV nephropathy have improved outcomes. Although no approved antiviral drug is available, leflunomide, cidofovir, quinolones, and intravenous Ig have been used. Retransplantation after BKV nephropathy has been successful.

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Polyomavirus infection in kidney transplant recipients is of increasing interest and research. Although the two human polyomaviruses, BK virus (BKV) and JC virus (JCV), were reported in 1971 (1,2), their influence and importance were limited. The emergence of polyomavirus nephropathy has coincided with the use of new potent immunosuppressive medications (3,4). It is usually associated with BKV, affects up to 8% of recipients, and frequently results in allograft loss or permanent dysfunction (5). It presents as an asymptomatic gradual rise in creatinine with a tubulointerstitial nephritis that mimics rejection, producing a treatment dilemma. The decrease in immunosuppression that is needed to treat infection is opposite to the increases that are needed to treat rejection.

Two studies in kidney transplant recipients who were treated with prednisone and azathioprine in the early 1980s have provided the foundation for much of our current understanding of polyomaviruses in transplant recipients. Hogan *et al.* (6) and Gardner *et al.* (7) found that the pretransplantation seroprevalence was 80 to 88% for BKV and 54 to 55% for JCV. The posttransplantation rates of polyomavirus infection were 18 to 44% for BKV and 30 to 35% for JCV. Most polyomavirus infections were asymptomatic and occurred within the first 3 mo after transplantation. BKV infection was associated with a rising creatinine. More than 20 yr ago, Gardner *et al.* (7) warned, "The detection of polyomavirus infection is important as increased immunosuppression needs to be avoided to prevent possible complications."

Epidemiology

Three polyomaviruses—JCV, BKV, and SV40—cause disease in humans. Humans are the natural host for JCV and BKV. On the basis of serology, BKV is acquired during childhood, and seroprevalence stabilizes or wanes with increasing age (8,9). In contrast, JCV seroprevalence increases with age. The route of the primary infection may be fecal-oral, respiratory, transplacental, or from donor tissue (10–13). Presumably, during a viremic phase, the virus infects target tissues, including the uroepithelium, lymphoid tissue, and brain (13,14), establishing a latent or permissively lytic infection. SV40, a simian virus, was introduced into the human population through contaminated polio and adenovirus vaccines (15). It can be acquired through close contact with nonhuman primates and may spread at a low rate from person to person (10,16,17). Although SV40 has been identified in kidney transplant biopsies and associated with native kidney diseases (18–21), its importance in kidney transplantation is poorly defined and is not discussed further.

Virology

BKV and JCV are small, nonenveloped viruses with an icosahedral capsid and a core of circular double-stranded DNA in association with histones (22). The genome is transcribed bidirectionally. It encodes for the early regulatory proteins—small t antigen and large T antigen—and the late structural proteins—VP1, VP2, and VP3. The genome also contains a noncoding control region that contains the origin of replication and transcription factor binding sites. The agnogene and its protein product help regulate the virus replication and disrupt host cell processes (23–25). The capsid consists of 72 pentamers, each with five VP1 proteins and a central VP2 or VP3 protein. VP1 binds the sialic acid residues of its receptor onto permissive cells (26). The gangliosides GD1b and GT1b and α(2,3)-linked sialic acids on N-linked glycoproteins can act as the receptor for BKV (27,28), whereas α(2,6)-linked sialic acids and the serotonin receptor 5HT2A can act as the receptor for JCV (29,30). After attachment, BKV is internalized *via* caveolae-mediated endocytosis, whereas JCV enters through a clathrin-dependent endocytosis (31,32). Once inside the cell, the viruses traffic to the nucleus and establish a latent or lytic infection. Although JCV resides in the uroepithelium (33) and commonly reactivates (6,7,34,35), it rarely causes nephropathy (36,37). Therefore, the remaining discussion focuses on BKV nephropathy.

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Pathogenesis

Replication of BKV occurs during states of immune suppression. BKV viruria occurs in pregnancy, cancer, HIV infection, diabetes, and transplantation (13). BKV viremia and BKV nephropathy, however, are rare outside of kidney transplantation. BKV viremia occurs in 13% and BKV nephropathy in 8% of kidney transplant recipients (5). In a kidney transplant recipient, BKV reactivation can come from the donor or the recipient. Recipients who had BKV infection and received a kidney from the same donor have been shown to have identical BKV genotypes, supporting donor transmission (12,38). Recipients whose donors had higher BKV antibody titers were more likely to develop BKV infection than those with lower titers, also supporting donor transmission (12,39). Injury is also believed to contribute to reactivation. In a mouse polyomavirus model, mechanical or chemical injury allowed for initiation of acute infection and also reactivation of latent polyomavirus (40). In humans, injury could come from ischemia or stent placement, or rejection could allow for new infection and reactivation of latent infection in either the donor or recipient.

Once the virus has reactivated, an ascending infection *via* cell-to-cell spread occurs (41–43). Without appropriate immunologic control, a progressive lytic infection ensues (44). This results in large nuclear and perinuclear virus-containing inclusions in the tubule cells. Lysis of these infected cells results in viral seepage into the tubule lumen and urine but also to the interstitium and propagation to surrounding cells. Subsequent tubular cell necrosis leads to cast formation and denudation of the basement membrane. Destruction of tubular capillary walls results in vascular spread of the virus. A heterogeneous interstitial infiltration of inflammatory cells as well as tubulitis may be absent, intermixed with the active infection, or noted in areas that lack cytopathic changes. Collateral damage with necrosis and apoptosis of noninfected tubule cells may occur. The resultant effect of continued intragraft inflammation, tubular injury, and upregulation of profibrotic mediators is allograft dysfunction and loss.

Early retrospective studies identified tacrolimus and mycophenolate mofetil (MMF) as risk factors for BKV nephropathy (4,43,45–47). More recent retrospective studies found BKV nephropathy associated with the combination of tacrolimus levels (>8 ng/ml) and MMF dosages (1.5 to 2 g/d) (48,49). BKV nephropathy, however, has been reported with triple drug regimens that include a calcineurin inhibitor (tacrolimus or cyclosporine), an adjuvant agent (MMF, azathioprine, or sirolimus) and prednisone (45,49–53), calcineurin-free triple drug therapy (54), double therapy with a calcineurin inhibitor and sirolimus (50,55), tacrolimus monotherapy (56), and with or without use of an induction agent (53). A prospective, randomized study showed that BK viruria and viremia were not different among those who received tacrolimus compared with cyclosporine, azathioprine compared with MMF, and rabbit-antithymocyte globulin induction compared with no induction (57). The highest rates of viruria and viremia were among those who received the combination of cyclosporine and azathioprine or tacrolimus and MMF. Taken together, these studies suggest that it is the net state of immunosuppression and not a specific drug that allows for development of progressive BKV infection.

Immunology

Although polyomavirus reactivation is common, clinically significant disease is unusual. This is because most recipients are able to control the viruses. Persistent viral infections, such as polyomaviruses, cannot be completely cleared and require continuous immune control (58–60). BKV replication typically begins early after transplantation and after treatment of rejection when immunosuppression is greater and immune control is reduced. The contribution of the humoral, cellular, and innate immune compartments to the control is not well known.

Although 60 to 80% of recipients are BKV seropositive before transplantation (5–7,39,57,61), the presence of these BKV-specific antibodies has not been shown to prevent development of BKV infection. However, BKV-specific antibodies can inhibit BKV infectivity (32,62), and a graded protective effect of the titer of recipient BKV-specific antibodies before transplantation has been suggested (63). BKV seronegativity is also a risk factor for BKV viruria (61) and nephropathy (64) in children. In adults, Shah (65) reported that seropositive donors and seronegative recipients (BKV D+/R−) developed a serologically defined BKV infection most frequently (43%). Bohl *et al.* (12) found that seropositive donor and recipients (BKV D+/R+) developed BKV viruria most frequently (50%). In both studies, only 10% of seronegative donors and recipients developed BKV infection. Thus, BKV antibodies may play a role in the immune response, but they also may indicate a risk for reactivation.

Reduction in immunosuppression results in a significant increase in BKV-specific IgG antibody titers (63,66,67), emergence of BKV-specific cellular immunity (66), clearance of viremia, and stabilization of graft function (57). The presence of BKV antibodies seems to have a limited role. Comoli *et al.* (66) found that despite persistently elevated BKV antibody titers, recurrent BKV viremia was associated with a low frequency of IFN-γ–producing cells. Chen *et al* (68) found that viremia and an elevated creatinine persisted in most recipients who had BKV nephropathy and developed high BKV antibody titers but weak cytotoxic T lymphocyte responses. However, in recipients with a strong cytotoxic T lymphocyte response but low antibody titers, viremia cleared and creatinine returned to the pre-BKV nephropathy baseline.

The cellular immune response may also contribute to allograft dysfunction. Mannon *et al.* (50) found that the RNA transcriptional profiles that were associated with BKV nephropathy indicated a more intense CD8 functional response and more profibrotic response than acute cellular rejection. Hammer *et al.* (69) found that recipients with viral loads >250,000 copies/ml had detectable BKV-specific $CD4^+$ T cells in peripheral blood, but only the two recipients with BKV-specific $CD8^+$ T cells >0.1% lost their allografts. The specificity of the cellular response may also be detrimental. Recipients with greater donor and recipient HLA mismatching had an increased incidence of BKV nephropathy (70), possibly mediated by more episodes of rejection, intense immunosuppression, and impaired cytotoxicity in an allogeneic environment but less allograft loss (71). This

suggests that lysis of allogeneic BKV-infected target cells is less efficient with HLA-unrestricted T cells than with HLA-restricted T cells. T cells recognize epitopes that are shared by JCV and BKV that may produce a cross-protective effect (72–74).

Diagnosis

The diagnosis and the severity of BKV infection correspond to our understanding of the pathogenesis of BKV nephropathy. Viral replication begins early after transplantation and progresses through detectable stages: Viruria then viremia then nephropathy (5,57,75–77) (Figure 1). Viruria can be detected by PCR for BKV DNA, reverse transcription–PCR for BKV RNA, cytology for BKV inclusion–bearing epithelial cells termed "decoy cells," or electron microscopy for viral particles (5,7,57,78). These tests are sensitive for detecting active BKV infections but lack specificity for nephropathy because the detected virus could originate anywhere along the urinary tract. Detection of BKV DNA in the plasma or of viremia may be a better indicator of nephropathy. As the infection intensifies, the markers of viral replication increase. Threshold values have been suggested to predict BKV nephropathy, but considerable overlap of these values exists among recipients without BKV nephropathy, active BKV nephropathy, and resolved BKV nephropathy (79) (Table 1), Therefore, a transplant kidney biopsy remains the gold standard for diagnosing BKV nephropathy. Importantly, the interstitial nephritis and tubular cytopathic changes of BKV nephropathy can be focal or isolated to the medulla and missed on one third of biopsies if only a single core is evaluated (80) (Figure 2). Therefore, at least two cores including medulla should be examined. If there are no cytopathic changes on routine histology but there is a high clinical suspicion, then adjunctive tests such as immunohistochemistry directed specifically against BKV or cross-reacting SV40 large T antigen should be performed because the histopathology of BKV infections may be misinterpreted (45). If the initial biopsy does not confirm BKV nephropathy, then preemptive treatment or repeat biopsy can be considered.

Histology

The characteristic findings on light microscopy are intranuclear basophilic and gelatinous-appearing viral inclusions in epithelial cells of the urothelium (46,47,80). These are found in the medulla or cortex and are multifocal with random distribution. Three histologic patterns (A, B, and C) have been described (80–82). In early disease (pattern A), the cytopathic changes are present with little to no inflammation or tubular atrophy. Pattern B consists of viral cytopathic changes with varying degrees of inflammation, tubular atrophy, and fibrosis. In late BKV nephropathy (pattern C), cytopathic changes often are less apparent as a result of a background of tubular atrophy, interstitial fibrosis, and chronic inflammatory infiltrate. The degree of damage corresponds to the degree of allograft dysfunction and allograft outcome (80) (Table 2). The distinction of BKV nephropathy from acute tubular necrosis, interstitial nephritis, and acute cellular rejection is difficult and aided by assessment of blood or urine PCR. Absence of definitive features of acute cellular rejection such as endotheliitis and absence of C4d deposits in peritubular capillaries are helpful. Other histopathologic changes include glomerular crescents (10 to 20%) (46,83), ischemic glomerulopathy (62%) (83), transplant glomerulopathy (62%) (83), abundant plasma cell infiltrates (up to 75%) (46,80,84), and tubular microcalcifications (25%) (81). Features of calcineurin inhibitor toxicity such as striped fibrosis (45,46,80,81), thrombotic microangiopathy (45,81), and tubular isometric vacuolization (81) may also be present.

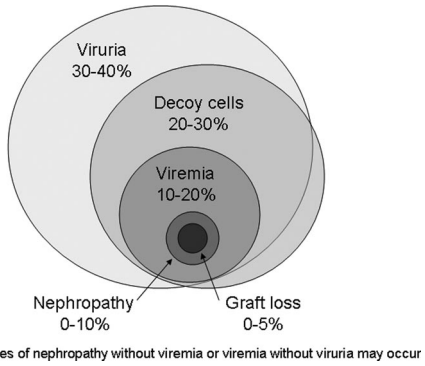

Figure 1. Type and prevalence of BK virus (BKV) infections in kidney transplant recipients.

Treatment

The principal treatment for BKV nephropathy is reduction in immunosuppression. Various strategies include reduction or discontinuation of the calcineurin inhibitor and/or adjuvant agent, changing from MMF to azathioprine, sirolimus, or leflunomide or from tacrolimus to cyclosporine (38,49,52,53,55,85–87). Importantly, BKV nephropathy seems to develop less frequently with maintenance protocols that involve steroid withdrawal (75,88). When BKV nephropathy is diagnosed early within the first 6 mo after transplantation and the creatinine is stable, survival is improved compared with when the diagnosis is made later and the creatinine is elevated.

Early or Presumptive BKV Nephropathy

Reduction in immunosuppression to clear the infection is balanced against the risk for precipitating acute or chronic rejection (Figure 3). Brennan *et al.* (57) showed that preemptive withdrawal of the antimetabolite upon detection of viremia prevented BKV nephropathy without significantly increasing the risk for rejection. Viremia cleared in 22 (96%) of 23 recipients with only one episode of acute rejection directly related to immunosuppression reduction. Of the 22 recipients whose viremia resolved, 32% cleared before protocol decreases in immunosuppression, 32% cleared after withdrawal of the antimetabolite, 9% cleared after reduction in the calcineurin inhibitor, and 27% required withdrawal of the antimetabolite followed by reduction in calcineurin inhibitor for persistent viremia. Prospectively screening pediatric recipients, Hymes and Warshaw (89) cleared viremia in 58% of recipients with presumptive nephropathy after a 50% reduction in the dosage of mycophenolate or sirolimus and targeting tacrolimus troughs of 3 to 5 μg/dl. With BKV nephropathy diagnosed on surveillance bi-

Table 1. Noninvasive tests for BKV nephropathy[a]

Diagnostic Test	Threshold Value	PPV (%)	NPV (%)
Plasma BKV DNA PCR (copies/ml) (5,43,79,89)	Presence to ≥10,000	50 to 85	100
Decoy cells (cells/cytospin)(5,43,81)	Presence to ≥10	27 to 90	99 to 100
Urine BKV DNA PCR (copies/ml) (79)	$\geq 1 \times 10^7$	67	100
Urine BKV mRNA RT-PCR (copies/ng total RNA) (78)	$\geq 6.54 \times 10^5$	75[b]	97[b]

[a]BKV, BK virus; NPV, negative predictive value; PPV, positive predictive value; RT-PCR, reverse transcription–PCR.
[b]Based on BKV nephropathy biopsy prevalence of 28.6%.

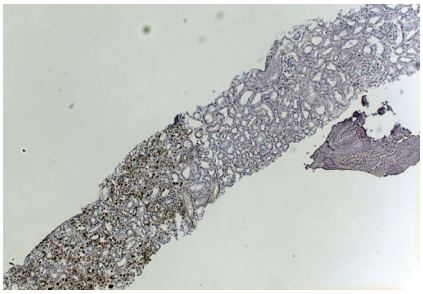

Figure 2. BKV nephropathy. Immunohistochemistry shows characteristic nuclear staining isolated to the medulla.

opsy before an elevation in creatinine, Buehrig *et al.* (51) found that creatinine remained stable and the number of BKV-positive tubules on follow-up biopsy significantly decreased after a step-wise reduction in MMF plus reduction in tacrolimus or conversion to cyclosporine. Conversion from tacrolimus to cyclosporine may lower MMF levels if dosages of MMF remain the same (90). It is interesting that cyclosporine *in vitro* but not tacrolimus *in vitro* has been shown to inhibit BKV reactivation (91). Although complete cessation of MMF may be necessary if viremia persists, MMF may limit proinflammatory and profibrotic cytokines (92,93).

Late BKV Nephropathy

The diagnosis of BKV nephropathy in the setting of allograft dysfunction often indicates more severe histologic changes, and renal function may only stabilize or may continue to progress despite treatment (48,49,51,53,79,80,86,94,95). Also, not treating or inadvertently treating with an antilymphocyte antibody often will lead to progression of disease (96). Whether to reduce or discontinue one or more components of the maintenance regimen is not clear (77,86,94). Ramos *et al.* (53) found no difference in graft survival whether immunosuppression was reduced or continued or between reduction and discontinuation of tacrolimus or MMF among 67 recipients with BKV nephropathy. Vasudev *et al.* (86) used an empiric immunosuppression scale based on drug dosage, not drug level, and found that improvement in renal function after diagnosis of BKV nephropathy correlated with reduction in the calcineurin inhibitor rather than total immunosuppression. Vasudev *et al.* (86) also found that renal function declined by 4.8 ml/min per mo before the diagnosis of BKV nephropathy and slowed to 0.7 ml/min per mo after a 40% reduction in overall immunosuppression. Renal recovery or stabilization was delayed and occurred at a median of 112 d after diagnosis. Thiry-six percent progressed to allograft loss. This was more common when the creatinine was >2.2 mg/dl at diagnosis. Rocha *et al.* (49) reported no allograft loss and clearance of viruria in seven patients after discontinuation of MMF and reduction in calcineurin inhibitor dosage despite a mean creatinine of 3.2 mg/dl at diagnosis compared with persistent viruria and allograft loss in two recipients after only reduction in MMF and modification of calcineurin inhibitor. Dosage reduction of the adjuvant agent and calcineurin inhibitor in pediatric patients failed to clear viremia with 50% graft loss (89). Dosage reduction of the adjuvant agent and calcineurin inhibitor in adults failed to improve tubular BKV burden with a rising mean creatinine (51). Josephson *et al.* (55) reported only a 15% allograft loss in recipients who had BKV nephropathy and were treated with discontinuation of MMF, dosage reduction of tacrolimus, and addition of leflunomide, an immunosuppressive drug that inhibits BKV, *in vitro*. However, several factors have limited enthusiasm for the use of this drug: (*1*) High dosages of leflunomide (≥40 mg/d) are required to afford efficacy, (*2*) the relationship between the drug dosage and level is unpredictable, (*3*) drug levels are not available, and (*4*) the immunosuppressive potency of leflunomide is weak and the effect that is seen from its use may simply reflect lower immunosuppression.

Adjuvant Therapies

On the basis of *in vitro* activity against BKV, cidofovir, quinolones, and intravenous Ig (IVIG) have been reported as treatment options for BKV nephropathy. Although cidofovir, a cytosine analogue and viral DNA polymerase inhibitor, inhibits BKV replication, the mechanism is unclear because BKV lacks a viral polymerase gene (97–99). Rather than a direct effect on BKV replication, cidofovir may restore the function of p53 and pRB, targets of the large T antigen, and permit BKV-infected cells to undergo apoptosis (22,99). When used for treatment of BKV nephropathy, cidofovir has been given at dosages ranging from 0.25 to 1 mg/kg every 1 to 3 wk with generally favorable results (55,89,95,100–108). However, most studies were observational, and cidofovir was used in conjunction with immuno-

Table 2. Histologic patterns of BKV nephropathy

Histologic Pattern	Biopsy Findings	Outcome (ESRD)[a]	Differential
A	Intranuclear viral inclusions Minimal inflammation tubular cell necrosis fibrosis	13%	Normal Coexisting diagnosis
B	Intranuclear viral inclusions Moderate to severe interstitial inflammation Tubular cell necrosis Minimal tubular atrophy and fibrosis	55%	Interstitial nephritis Acute tubular necrosis Acute rejection
C	Intranuclear viral inclusions Moderate to severe tubular atrophy and fibrosis	100%	Chronic allograft nephropathy

[a]Modified from Li *et al.* (74).

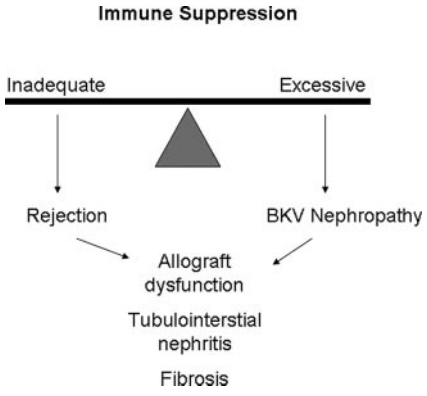

Figure 3. Impaired immune suppression balance. Inadequate immune suppression results in rejection, whereas excessive immune suppression results in BKV nephropathy. Both conditions present as allograft dysfunction with tubulointerstitial nephritis and progression to fibrosis.

suppression reduction. In a cohort of 21 recipients with BKV nephropathy, Kuypers *et al.* (102) reported no graft loss in eight recipients who agreed to treatment with cidofovir but a 70% graft loss in the 13 who did not receive cidofovir. Cidofovir should be used with caution, frequent monitoring, and informed consent because of the potential complications (109,110).

Quinolones, DNA gyrase inhibitors, may interfere with the large T antigen helicase activity (111) and have *in vitro* and *in vivo* activity against BKV (112–114). Two months after a 10-d course of gatifloxacin, seven of 10 recipients with active BKV replication had reduction in viremia or urinary decoy cells (115). Thamboo *et al.* (116), however, did not find improvement in viral clearance after a 10-d course of ciprofloxacin.

IVIG has been used for treatment for BKV nephropathy because of its immunomodulatory (117) as well as potential anti-BKV properties (118). Although IVIG contains BKV-specific antibodies, seropositive recipients as well as recipients with active BKV infections may have high BKV-specific antibody titers, suggesting that antibody-mediated neutralization does not contribute to viral control. Nevertheless, in combination with immunosuppression reduction, IVIG (2 to 3.5 g/kg over 2 to 7 d) treatment was used as initial treatment for BKV nephropathy (119,120) and BKV nephropathy with concurrent acute rejection (95). Although Sener *et al.* (119) reported that only one (13%) of eight recipients who were treated with IVIG returned to dialysis, half had persistent viremia. Wadei *et al.* (95) found that compared with unmatched control subjects who were not treated with IVIG, IVIG treatment did not improve graft survival. Because of the cost (121), potential adverse effects (122), and unproven efficacy, IVIG use for BKV nephropathy should be limited until controlled studies suggest benefit.

Postinfection Monitoring

Failure to clear BKV leads to worse graft function and outcomes. Because histologic clearance of the virus (79) and disappearance of decoy cells (87) precede clearance from the blood, monitoring should be performed with quantitative assays, preferably BKV PCR, until the viral level is undetectable or at least falls below the threshold value that is associated with BKV nephropathy. On the basis of kinetic models (123) and prospective monitoring (57,79,87,123), viremia clears in 7 to 20 wk, but the initial decrease may be delayed by 4 to 10 wk after immunosuppression reduction. If viremia persists, then further reduction of current maintenance therapy, conversion to sirolimus, or addition of leflunomide can be considered. Twelve weeks after the initial immunosuppression reduction, Wali *et al.* (87) described three recipients who had persistent viremia and responded to further reduction in immunosuppression by conversion to sirolimus (target level 10 to 12 ng/ml) and low-dosage prednisone (2.5 mg every other day).

Retransplantation

BKV nephropathy shortens allograft survival. Tubulointerstitial damage from direct and indirect effects of the virus and rejection after immunosuppression reduction lead to early graft

loss or chronic dysfunction (46,48,51,53,80,86,94,95,124). In recipients who have advanced kidney disease or who have returned to dialysis from BKV nephropathy, retransplantation has been successful (125–130). In most cases, transplant nephrectomy and/or studies to confirm no active viral replication have been performed. However, in the setting of active viremia, viral levels become undetectable within 14 d after preemptive retransplantation with simultaneous allograft nephrectomy despite antibody induction (129). BKV viruria (131), viremia (129), nephropathy (128,132), and graft loss (132) can recur. Because of the long duration after transplantation, intervening negative studies for BKV, and genomic differences, these recurrent BKV infections likely reflected new BKV infections. Therefore, BKV nephropathy is not a contraindication for retransplantation but has recurred in two (12%) of 17 reported recipients. Allograft nephrectomy may not be necessary. In the setting of active viral replication, it seems prudent. Evidence of BKV-specific immunity can be evaluated before retransplantation (125) but in the setting of a resolved infection can be inferred. However, for preemptive transplantation in recipients of combined organ transplants, for whom reduction in immunosuppression is limited, evidence of no active viral replication or BKV-specific immunity should be determined.

BKV Nephropathy and Acute Rejection

The treatment of recipients whose biopsy shows rejection with concurrent BKV nephropathy or early after reduction of immunosuppression to treat BKV nephropathy remains problematic. More than half of biopsies may show tubulitis (5,43,47,80), and reduction in immunosuppression can precipitate rejection in 10 to 30% of recipients (51,53,57,86,108,124). The infiltrating mononuclear cells may represent a BKV-specific and/or allospecific response, and treatment is debatable (133,134). Studies that compared BKV nephropathy with acute rejection have identified differences in the proportion and type of infiltrating cell (80,84,85), protein expression (43,80) and proteomic profiles (135), and gene expression profiles (50). However, these differences have not been characterized serially after modification in immunosuppression. Clinically, reports have described improved, stable, and worse graft function after steroid pulses (5,45,51,94). Comparing recipients who initially received increased immunosuppression with those whose immunosuppression was decreased, Celik *et al.* (94) found no significant short- or long-term improvement in tubulitis or creatinine with brief steroid therapy. On biopsies that were performed within the first 8 wk, the histologic viral load had improved significantly with initially decreased compared with increased immunosuppression but was similar on later biopsies. Therefore, in contrast to others (82), we favor initial reduction in immunosuppression without a steroid pulse. However, the presence of atypical features such as strong peritubular capillary C4d staining, vasculitis, glomerulitis, or interstitial hemorrhage would support rejection (84,136) and require an individualized approach. The delayed improvement in creatinine after reduction in immunosuppression likely reflects the slow resolution of the cellular infiltrate. On follow-up biopsy, we consider a cellular infiltrate with or without tubulitis in the setting of persistent BKV viremia consistent with resolving BKV nephropathy and continued monitoring. McGilvray *et al.* (137) found severe tubulitis, mild intimal arteritis, and no viral inclusions on a biopsy 1 mo after reduction in immunosuppression. Despite no adjustment to immunosuppression, the patient's creatinine gradually improved. Once BKV nephropathy and viremia have cleared, the benefit of uptitrating immunosuppression to prevent chronic rejection or late acute rejection remains unknown.

Screening

It has been recommended that screening for BKV should be performed every 3 mo for the first 2 yr after transplantation, then annually through the fifth year, when allograft dysfunction occurs and when a transplant kidney biopsy is performed (82). Screening should be based on a urinary assay for decoy cells, BKV DNA, or BKV RNA. A positive screening test should be confirmed within 4 wk along with a quantitative assay. Recipients with persistent high viral levels for >3 wk should undergo biopsy and intervention. Monitoring should continue every 2 to 4 wk until the viral level falls below threshold values and preferably to undetectable levels.

These recommendations are guidelines and should vary on the basis of assay availability and cost, recipient risk, and local incidence of BKV nephropathy. With a low incidence of BKV nephropathy, high false-positive testing rates, or high occurrence of acute rejection or chronic allograft dysfunction after reduction in immunosuppression, screening could produce greater cost and harm than not screening (138). Screening protocols should be used in centers with higher incidences of BKV nephropathy, using triple-drug therapy including tacrolimus and MMF, and with clinical trials to evaluate new therapeutic agents.

At our institution, we screen plasma monthly for the first 6 mo and at months 9 and 12 after transplantation, at the time of a transplant kidney biopsy, and after augmentation in immunosuppression (Figure 4). BKV viremia with stable allograft function triggers empiric immunosuppression reduction and continued monitoring, with the realization that viral levels should decline and clear within 1 to 6 mo (57). An allograft biopsy is performed for allograft dysfunction or persistent high-level viremia. This strategy has resulted in only one case

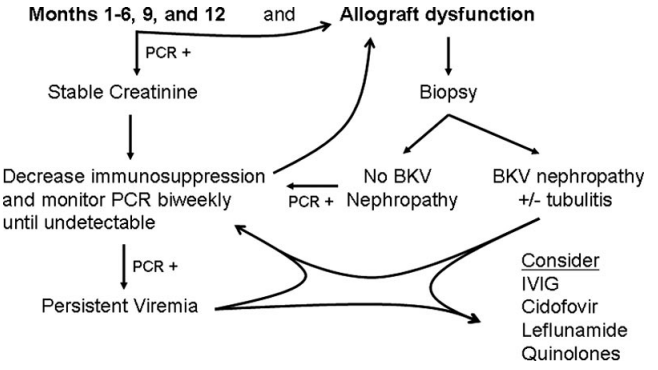

Figure 4. Screening protocol based on plasma BKV DNA PCR.

of BKV nephropathy in >700 new transplants in the past 5 yr, with an overall acute rejection rate of <10% at 1 yr.

Conclusion

BKV nephropathy remains a significant posttransplantation complication. Modern potent immunosuppressive medications have reduced acute rejection rates, improved early kidney allograft survival, and expanded the potential transplant population. For an individual recipient, however, the increased immunosuppression may be excessive and predispose to BKV nephropathy. No clinical risk factors clearly identify the recipients who will develop BKV nephropathy. Screening all recipients for replication of BKV and targeted reduction of immunosuppression can resolve the infection with stable renal function. However, this method of early detection and treatment is costly, compliance dependent, and potentially detrimental. Once a tubulointerstitial nephritis has developed, progression or resolution to tubular atrophy and interstitial fibrosis results in permanent allograft dysfunction. Treatment of BKV nephropathy is problematic. No antiviral medication is approved, and none has been appropriately studied in a randomized manner. Decreasing immunosuppression to allow a BKV-specific immune response to control the infection is the principle treatment. One potential consequence is the development of an allospecific immune response and rejection. Because monitoring for BKV-specific immunity is not widely available, monitoring for declining viral loads is used as a surrogate. With diffuse parenchymal involvement, resolution of viremia and improvement in creatinine may not occur for months. Although BKV infection is an area of active investigation in kidney transplantation, much of the data are derived from retrospective case-control studies. Prospective, randomized studies to address immunosuppression protocols, immune monitoring for BKV-specific and allospecific responses, and treatment protocols are needed. Until reliable measures of immunosuppression or novel agents that specifically target BKV are available, BKV infections in kidney transplantation will remain a challenge.

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Disclosures

None.

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