

BK nephropathy in the native kidneys of patients with organ transplants: Clinical spectrum of BK infection

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Abstract

Nephropathy secondary to BK virus, a member of the *Papoviridae* family of viruses, has been recognized for some time as an important cause of allograft dysfunction in renal transplant recipients. In recent times, BK nephropathy (BKN) of the native kidneys has been increasingly recognized as a cause of chronic kidney disease in patients with solid organ transplants, bone marrow transplants and in patients with other clinical entities associated with immunosuppression. In such patients renal dysfunction is often attributed to other factors including nephrotoxicity of medications used to prevent rejection of the transplanted organs. Renal biopsy is required for the diagnosis of BKN. Quantitation of the BK viral load in blood and urine are surrogate diagnostic methods. The treatment of BKN is based on reduction of the immunosuppressive medications. Several compounds have shown antiviral activity, but have not consistently

shown to have beneficial effects in BKN. In addition to BKN, BK viral infection can cause severe urinary bladder cystitis, ureteritis and urinary tract obstruction as well as manifestations in other organ systems including the central nervous system, the respiratory system, the gastrointestinal system and the hematopoietic system. BK viral infection has also been implicated in tumorigenesis. The spectrum of clinical manifestations from BK infection and infection from other members of the Papoviridae family is widening. Prevention and treatment of BK infection and infections from other Papovaviruses are subjects of intense research.

Key words: BK viral infection; BK nephropathy; Cardiac transplant; Bone marrow transplant; Liver transplant; Pancreatic transplant; Lung transplant

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Core tip: BK virus (BKV) is a member of a family of viruses that cause various diseases in animals and humans. Severe disease in transplanted kidneys was the first recognized human disease caused by BKV. In more recent times, BKV was also recognized as a cause of disease in the native kidneys of patients who had received bone marrow, heart, lung, liver and pancreas transplants, as well as in the kidneys of patients with loss of resistance to infection, such as patients with acquired immune deficiency syndrome or patients treated for malignant tumors. In addition to disease of the kidneys, BKV has also caused severe disease of the urinary bladder, the brain, the lungs, the gut and the blood. The diagnosis and particularly the management of infection by BKV present difficulties. Research for new medications specific for treating this infection is imperative.

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INTRODUCTION

BK virus (BKV) is a human polyomavirus identified in 1971 when it was isolated from the urine of a Sudanese kidney transplant recipient with renal failure secondary to distal ureteral stenosis^[1]. It belongs to the *Papovaviridae* family of viruses^[2]. BKV along with other papovaviruses, *e.g.*, JC virus (JCV), can cause disease in humans^[3,4]. BKV is ubiquitous in the general population and serologic studies suggest that primary infection occurs in early childhood at a median age of 4-5 years^[5,6]. BKV primary infection usually results in upper respiratory symptoms with rare reports of acute

cystitis^[5,6]. The route of transmission is not conclusively known. It is believed that transmission occurs *via* the respiratory pathway^[5,6].

Latent infection with BKV typically causes clinical disease in the genitourinary tract since the virus has a tropism for renal tubular and transitional epithelial cells. In these cells BKV establishes a life-long latency^[3,4,7]. Viral reactivation usually occurs in patients with immunosuppressed states resulting in viruria. A small percentage of patients with viruria develop an invasive infection of the kidney^[3]. BKV infections involving the urinary tract were the first to be reported in kidney transplant recipients and are the most frequent manifestations of BKV. BKV infection in other organs is less frequent^[2,3,8].

BK nephropathy (BKN) was recognized as an emerging problem in renal transplant recipients with the introduction of improved immunosuppressive treatments such as tacrolimus, mycophenolate, and antilymphocyte globulins^[6,7,9]. Renal transplant failure rates, due to BKN, especially if diagnosed late, can reach as high as 50%-80% within 24 mo^[7]. Therefore screening for BKV in renal transplant recipients has become routine^[2,9]. Costa *et al*^[10] reviewed the clinical and histologic features, diagnosis, monitoring of the virology and immunological picture and treatment of BKN. Their review was based primarily on reports of BKN involving renal allografts^[10].

In recent years, reports of BKN in native kidneys and of BKV infection in other organ systems have emerged with increasing frequency in non-renal solid organ and bone marrow transplant patients^[2,5,7,8,11] as well as in other immunosuppressed patients. The main purpose of this review is to summarize the clinical characteristics, diagnosis, pathophysiology and treatment of BKV infection in patients with solid organ and bone marrow transplantation. The spectra of manifestations of BKV infection and of patient groups developing BKV infection are enlarging. In addition to BKN in native kidneys of transplant recipients, this report will also address manifestations of BKV infection outside the urologic system and in patients without organ transplants. Several aspects of BKV infection, particularly the diagnosis, pathogenesis, and treatment of BKN have been studied extensively in kidney transplant recipients. This review will therefore include relevant studies of renal transplant recipients in these three areas.

The review has three major parts: (1) clinical manifestations of BKV infection; (2) diagnosis of BKN and pathogenesis of BKV infection; and (3) treatment of BKV infection and human diseases secondary to other members of the Papovavirus family. Key points of each major part will be presented at its end.

PART A CLINICAL MANIFESTATIONS OF BKV INFECTION

Two cases will illustrate the clinical features and histology of BKN in native kidneys of transplant recipients.

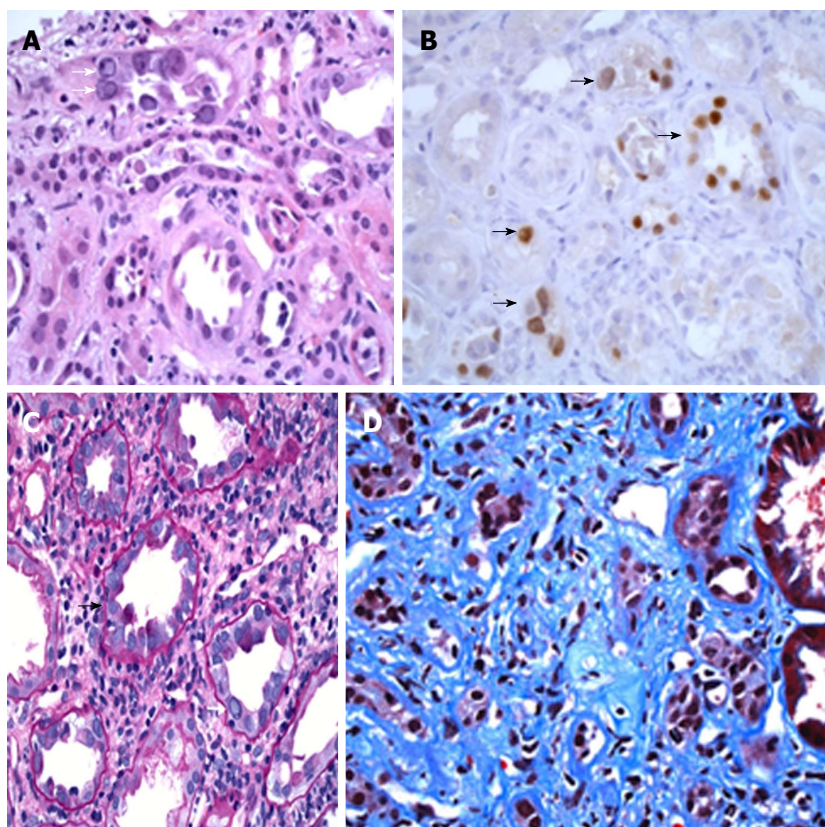


Figure 1 BK nephropathy in the native kidneys of a lung transplant recipient (Patient 2 in this report, A and B) and in the native kidneys of a bone marrow recipient (patient 1 in this report, C and D). Kidney biopsy showing BK nephropathy (BKN), taken from a 70-year-old male with a history of lung transplantation for pulmonary fibrosis. A renal biopsy was performed because of significant worsening in renal function over a one-month period. A: Kidney biopsy showing active BK virus infection of renal tubules, with multiple homogeneous-appearing viral nuclear inclusions (white arrows), and features of associated acute tubular injury, including sloughing of tubular cells (H and E stain, 400 × magnification); B: Multiple renal tubules show positive nuclear staining for the SV40 large T antigen by immunoperoxidase staining (black arrows), confirming infection of tubular cells by polyomavirus (400 × magnification); Kidney biopsy from a 30-year-old male with a history of an allogeneic bone-marrow transplantation for aplastic anemia, who developed sequentially post-transplant Epstein-Barr virus associated large B-cell lymphoma, graft vs host disease and progressive elevation of his serum creatinine. This patient died from pneumococcal pneumonia and invasive aspergillosis two months after the diagnosis of BKN; C: Biopsy of renal cortex showing mononuclear tubulitis (black arrow), intranuclear BK virus inclusions (white arrow), and a prominent interstitial chronic inflammatory infiltrate (PAS stain, 400 × magnification); D: Another area of the biopsy shows extensive interstitial fibrosis and tubular atrophy, consistent with late changes secondary to infection (Trichrome stain, 400 × magnification).

Patient 1

A 30-year-old Hispanic man received a matched allogeneic bone marrow transplant from an unrelated donor approximately two years after the diagnosis of aplastic anemia. Six months after the transplant he developed post-transplant lymphoproliferative disorder (Epstein Barr Virus associated diffuse large B cell lymphoma of the right tonsil). He underwent tonsillectomy, localized radiation, and one cycle of CHOP (cyclophosphamide, adriamycin, vincristine, prednisone) followed by two treatments with rituximab.

Two years after transplantation he developed graft vs host disease of his esophagus and small intestine which required initiation of immunosuppressive therapy. He was placed on tacrolimus. After ten months, tacrolimus was tapered and sirolimus was started because of concern for calcineurin inhibitor toxicity. After three months sirolimus was replaced by mycophenolate mofetil because his graft vs host disease was not improving.

The patient's serum creatinine was 0.7-0.9 mg/dL

pre-transplant and 1.2 mg/dL prior to the initiation of tacrolimus. Renal function worsened while he was on tacrolimus, which was discontinued when the serum creatinine reached 2.0 mg/dL. All blood tacrolimus trough levels were between 2 and 3 ng/mL. Despite discontinuation of tacrolimus, the patient's renal function continued to decline. Approximately four years following the bone marrow transplant, his serum creatinine was 3.15 mg/dL (estimated glomerular filtration rate by CKD-EPI equation of 25 mL/min per 1.73 m²). Urine microscopy was bland and urine protein to creatinine ratio was 0.6 g/g. Renal ultrasound was unremarkable. Serum antinuclear antibodies, antineutrophil cytoplasmic antibodies (ANCA), hepatitis panel, and human immunodeficiency virus (HIV) test were negative. Serum complement levels (C₃, C₄) were normal. Serum BK viral load was 700000 copies/mL.

Percutaneous renal biopsy demonstrated morphologic features consistent with BKN. Light microscopy was notable for lymphocytic tubulitis and viral nuclear inclusions (Figure 1C and D). Immunohistochemical

staining for SV 40 large T antigen showed positivity in tubular nuclei. There were no specific findings on immunofluorescence or electron microscopy.

The patient's BKN was treated with ciprofloxacin only because immunosuppression could not be lowered given his graft vs host disease and leflunomide could not be used due to preexisting leukopenia. During treatment with ciprofloxacin renal function and BKV titer continued to worsen. One month after the start of ciprofloxacin treatment, the patient was hospitalized with pneumococcal pneumonia and invasive aspergillosis. He became progressively septic and died one month later.

Patient 2

A 70-year-old Caucasian male with history of pulmonary fibrosis due to usual interstitial pneumonitis underwent a left sided lung transplant. His immunosuppressive regimen included tacrolimus, mycophenolic acid and prednisone. One year following the lung transplant, he suffered unprovoked pulmonary embolism and has remained on anticoagulation with warfarin since then. Serum creatinine levels were stable at 1.0-1.1 mg/dL until two years following the lung transplant when they began to rise. BK viremia was detected and mycophenolic acid was discontinued. However, renal function continued to decline and serum creatinine reached 3.0 mg/dL. His blood tacrolimus levels were between 5 and 8 ng/mL.

Urine microscopy was bland. Renal ultrasonogram demonstrated normal sized kidneys with multiple bilateral simple cysts. Serum BKV level was 10 million copies/mL. Renal biopsy showed active BKN, with visible viral inclusions, positive tubular nuclear staining for SV-40 large T antigen, and associated tubular cell injury/necrosis and mainly mononuclear tubulitis (Figure 1A and B). There was moderately severe interstitial fibrosis and tubular atrophy (about 40%-45%) and global glomerulosclerosis (13%). There were no specific findings on immunofluorescence microscopy.

Following the renal biopsy, administration of tacrolimus and prednisone was continued and Leflunomide was started at a dose of 10 mg daily and was slowly titrated up to 20 mg daily two months later. He also received three monthly doses of intravenous immunoglobulin (IVIG) at a dose of 1 g/kg. However, despite improved BK viral titers (from 10 million to 3.5 million copies/mL), his serum creatinine continues to range between 2.8 and 3.0 mg/dL.

GENERAL CONCEPTS OF BKV INFECTION IN PATIENTS WITH ORGAN TRANSPLANTS

Evolution of BKN in kidney transplant recipients^[12-22]

An early study by Hogan *et al*^[12] detected polyomavirus excretion in the urine in 20% of renal transplant recipients. Approximately equal numbers of patients

with viruria excreted JCV and BKV. The same study reported a tendency to more frequent complications related to the renal graft in patients with documented viral replication^[12]. Subsequently, Rosen *et al*^[13] described the development of tubulointerstitial nephritis secondary to BKV in a 6-year-old boy with a renal transplant. A few years later Randhawa *et al*^[14] calculated that the incidence of BKN in renal transplant recipients was as high as 5%. Shinohara *et al*^[15], using a BKV-specific antibody, found that the virus was localized in renal calyces, renal pelvis, ureter and the urinary bladder. These findings are consistent with the clinical manifestations of BKV infection in the urinary tract.

Hirsch *et al*^[16] reported associations of BKN with high BK viral loads in the plasma of renal transplant recipients and with treatment for rejection, particularly with corticosteroids. Additionally, Hariharan^[17] computed a high incidence (between 30% and 60%) of irreversible renal transplant failure in patients with BKN. Bohl *et al*^[18] stressed the association between potent immunosuppression and BKN in renal transplant recipients and the need for screening for early detection and prevention of BKN.

In an analysis of a large cohort of renal transplant recipients reported to the Organ Procurement Transplant Network national registry of the United States, Dharnidharka *et al*^[19] found an increasing Kaplan-Maier incidence of BKN with time and a higher risk of BKN with immunosuppressive regimens that included rabbit antithymocyte globulin and tacrolimus/mycophenolate combinations. Subsequently, the same group^[20] stressed the risks of over-immunosuppression in respect to BKV infection and the lack of optimal methods for treating BKN. Nickleleit *et al*^[21] reviewed recent developments in the diagnosis of BKN, including noninvasive diagnostic procedures, and the expanding role of polyomaviruses in oncogenesis in patients with organ transplants. Sawinski *et al*^[22] identified male gender, advanced age of the recipient, previous rejection episodes, severity of leukocyte antigen mismatching, long cold ischemia time, serology for BKV and ureteral stent placement as additional risk factors for BKN.

Evolution of the concepts of BKN in native kidneys and of other manifestations of BKV infection^[2,23-37]

The manifestations of BKV infection from the urinary tract may differ between transplanted organ recipients. BKN and ureteral stenosis were identified as the cardinal manifestations of BKV infection in kidney transplant recipients and hemorrhagic cystitis was recognized as a cardinal manifestation of BKV infection in recipients of bone marrow transplants^[23-25]. The documented sites of BKV-associated disease include the urinary system, the lungs, the eyes, the brain, the retinae and the blood vessels^[24].

Rates of BK viruria and viremia in recipients of organ transplants were reported from several geographical sites. In a study from Madrid^[26], viruria was detected in

26.5% of kidney transplant recipients, 25.5% of heart recipients and 7.8% of liver recipients, while viremia was found in 12.2% of kidney recipients and 7.0% of heart transplant recipients. In Pittsburgh, BK viruria was detected in 8.7% of non-immunosuppressed controls, 34.9% of renal transplant recipients and 15.9% of liver transplant recipients, while BK viremia was detected only in renal transplant recipients (7.7%)^[27]. In the same study, the BK viral load in urine was higher in the kidney transplant patients than in the liver transplant recipients or control patients; interestingly, JC viruria was observed in 34.7% of controls, 22.3% of renal transplant patients and 22.7% of liver transplant recipients. JC viremia was not detected in any group.

In a study from Mayo Clinic, Rochester, Minnesota and University of Toronto, Ontario^[28], combined BK and JC viremia was found in 26% of kidney transplant patients, 7% of heart transplant patients and 4% of liver transplant recipients. In the same study, BK viremia was associated in certain instances with renal transplant rejection. A study combining findings from Philadelphia, Pennsylvania, and Seattle, Washington^[29], found a 15% incidence of BK viruria in 34 recipients of lung, liver, heart, and heart-lung transplants with chronic renal dysfunction. In contrast, a study from Alberta, Edmonton^[32], which also found an incidence of BK viruria in recipients of heart, liver or lung transplants, reported no association between renal dysfunction and BK viruria.

Sharma *et al.*^[34] presented the histological features of BKN, combined in one case with focal medullary JC viral co-infection, in patients with hematologic malignancies, with and without bone marrow transplants, or lung transplants. Several reviews^[2,7,30,31,33,35,36] addressed the manifestations and pathogenesis of BKV infection. Finally, a recent systematic review^[37] analyzed a large number of studies of BKV infection in non-renal solid organ transplant recipients. This study concluded that BK viremia was lower in non-renal than in renal transplant recipients and that BKN is rare in non-renal transplant recipients. In non-renal organ transplant recipients, overall incidence of BK viruria was 20% and incidence of BK viremia was 3%, with the highest incidence of BK viremia and BKN found in heart transplant recipients^[37].

URINARY MANIFESTATIONS OF BKV INFECTION IN PATIENTS WITH BONE MARROW OR STEM CELL TRANSPLANTS AND SOLID TRANSPLANTS OTHER THAN KIDNEY

Table 1 shows the reported organ transplants, other than solitary kidney transplants, in which clinical manifestations of BKV infection have been described. An extensive list of references is attached to each transplanted organ with BKV infection indicating the

Table 1 BK infection studies in organ transplants other than solitary kidney transplants

Transplanted organ	Ref.
Bone marrow, stem cells	[2,5,8,39-81]
Heart	[11,82-96]
Lung	[97-102]
Liver	[103-113]
Pancreas, combined pancreas-kidney	[114-135]

rising interest in this topic.

BK viral infections in the urinary system of recipients with bone marrow or stem cell transplants^[2,5,8,38-81]

Hemorrhagic cystitis has been a frequent and serious complication of bone marrow transplantation. This condition had been attributed to the use of cyclophosphamide. Arthur *et al.*^[38] reported a substantially higher frequency of BK viruria in patients who developed hemorrhagic cystitis compared to those who did not develop hemorrhagic cystitis after bone marrow transplantation. They also identified a temporal association between the development of BK viruria and the onset of hemorrhagic cystitis. Bedi *et al.*^[41] concluded that prophylactic treatment with MESNA and forced diuresis directed at cyclophosphamide toxicity failed to prevent hemorrhagic cystitis in patients with BK viruria.

Subsequently, a large number of publications^[5,39,41,43-45,47-50,52,53,55-57,59,61,62,66-68,71,75] provided firm evidence linking BKV infection and hemorrhagic cystitis in bone marrow or stem cell recipients and addressed various aspects of this syndrome.

Peinemann *et al.*^[45] reported that hemorrhagic cystitis in pediatric bone marrow transplant recipients is characterized by delayed onset, prolonged duration, viral reactivation and use of high doses of the alkylating agent busulfan. Bielorai *et al.*^[46] described patients with BKV-induced hemorrhagic cystitis triggered by cytomegalovirus (CMV) reactivation. Giraud *et al.*^[57] reported that the frequency of BK viruria and hemorrhagic cystitis was reduced in bone marrow recipients with related donors and in those receiving reduced intensity conditioning for the bone marrow transplant. The data analyzed by Koskevu *et al.*^[71] suggest that BKV hemorrhagic cystitis may result from nosocomial transmission in pediatric bone marrow transplant recipients with very low or undetectable BKV antibodies. These authors raised the issues of infection control and prophylactic use of cidofovir.

Various malignancies and aplastic anemia were frequent underlying diseases leading to bone marrow transplantation in the reports of BKV hemorrhagic cystitis. Hereditary hematological diseases, including thalassemia and sickle cell anemia were reported in a few instances^[66]. The severity of BKV hemorrhagic cystitis varies. Patients with life-threatening blood loss from hemorrhagic cystitis require drastic surgical interventions. Sébe *et al.*^[48] reported successful treatment of life-threatening blood loss by subtotal cystectomy in

Table 2 BK nephropathy in recipients of bone marrow or stem cell transplants

Ref.	Gender age	Renal function	Clinical associations
[8]	Female 36 yr	ESRD Dialysis	Relapsed Hodgkin's lymphoma
[8]	Female 43 yr	ESRD Dialysis	Acute myelogenous leukemia
[11]	Male 47 yr	ESRD Dialysis	Non-Hodgkin's lymphoma
[49]	Male 17 yr	ESRD Dialysis	Myelodysplastic syndrome Severe hemorrhagic cystitis No renal biopsy Death from multi-organ failure
[50]	Female 28 yr	ESRD Dialysis	Acute myelogenous leukemia Recurrent CMV reactivation
[51]	NR NR	ARF	Underlying disease NR Adenovirus pneumonia Adenovirus nephritis Death
[58]	Male 14 yr	Rising SCr	Acute myelogenous leukemia Death from multi-organ failure
[60]	Male 10 yr	GFR normalized	Acute myelogenous leukemia No renal biopsy
[63]	Male 51 yr	ESRD Dialysis	Myelodysplastic syndrome Hepatorenal syndrome GVHD Death from <i>Pseudomonas</i> sepsis
[64]	Male 10 yr	Peak SCr 3.5 mg/dL Scr at 1.7 mg/dL post-treatment	Chronic myelogenous leukemia Adenovirus and bacterial infections Severe GVHD
[64]	Male 13 yr	ESRD Declined dialysis	Fanconi's anemia Gram-positive bacteremias Pulmonary aspergillosis Hyperacute GVHD Death
[70]	Female 10 yr	ESRD Dialysis	Recurrent metastatic neuroendocrine tumor Thrombocytopenia, leukopenia, lymphopenia Antineutrophil-antiplatelet antibodies Death from sepsis
[75]	Female 10 yr	Peak SCr 1.58 mg/dL SCr at 1.1-1.4 mg/ dL post-treatment	Myelodysplastic syndrome Acute GVHD
[77]	Male 59 yr	CKD stage 5 not requiring dialysis	Myelodysplastic syndrome
[79]	Male 58 yr	Death due to sepsis eGFR stable at 20 at the time of death	Large B cell lymphoma Acute GVHD

BK nephropathy was manifested at various times post-heart transplantation. Ages reported in this Table are the calculated ages at the time of diagnosis of BK nephropathy. ESRD: End-stage renal disease; ARF: Acute renal failure; SCr: Serum creatinine; GFR: Glomerular filtration rate; GVHD: Graft vs host disease; NR: Not report.

patients with BKV hemorrhagic cystitis.

The level of BK viruria^[40,54,65,72,74,80] and plasma loads of BKV DNA^[76] predict clinical manifestations of BKV infections, including hemorrhagic cystitis. However, BKV infection is not the only, or even the more common, cause of hemorrhagic cystitis^[43]. Use of busulfan^[44] and adenovirus infection^[46] were also identified as other

important causes of this entity.

Other manifestations from the urinary system of BKV infection in bone marrow or stem cell recipients include ureteritis with ureteral stenosis^[78,80] and BKN^[8,11,49,50,51,58,60,63,64,70,75,77,79]. One report^[69] reviewed the features of BKN in bone marrow transplant recipients. Table 2 summarizes reported cases of BKN in recipients of bone marrow or stem cell transplant recipients. The majority of subjects developed end-stage renal disease (ESRD) and were placed on dialysis. Mortality was high in this patient sample. De laCruz *et al*^[73] reviewed the clinical manifestations of BKV infection in hematopoietic stem cell transplantation.

BK viral infections in the urinary system of recipients of heart transplants^[11,82-96]

Table 3 summarizes reported cases of BKN in cardiac transplant recipients^[11,84,85,86,89,90,91,93,94,96]. Rejection episodes of varying severity and frequency requiring increased immunosuppressive medications were reported in nine patients and ESRD in eight. Six patients underwent dialysis and three patients died. Lorica *et al*^[94] describe two additional pediatric heart transplant recipients with BKN. A three-month-old girl was on peritoneal dialysis at the time of the report while a 3-year-old girl on peritoneal dialysis died from BK encephalomyelitis^[94]. Thus, BKN has severe adverse effects on both renal function and overall state of health in cardiac transplant recipients. Persistent detection of the characteristic decoy cells in the urine indicating persistent BKV infection without any evidence of clinical manifestations was reported in one heart transplant recipient^[83].

Puliyanda *et al*^[88] compared the incidence of BK viremia and the risk of BKN in patients with isolated kidney, heart, liver, and combined kidney-heart, kidney-liver, kidney-pancreas and kidney-heart-liver transplant recipients. These authors concluded that the risk of BKN is lower in patients with isolated heart or liver transplants than in those with kidney transplants. High levels of BK viremia were associated with BKN in this study. However, none of the patients with heart transplants exhibited BK viruria and the plasma levels of BKV were low in liver transplant recipients.

Ducharme-Smith *et al*^[95] found BK viruria in approximately one third and BK viremia in only 7% of pediatric heart transplant recipients. One of the viremic patients developed BKN. Multivariate analysis identified history of Epstein-Barr infection as the only predictor of BK viruria in the same study^[95]. In another study, Pendse *et al*^[87] found definitive evidence of BK viruria in 13% of the heart transplant recipients but no signs of BKN. These authors proposed that a second organ-specific insult to the kidneys is needed for patients with BK viruria to develop BKN.

BK viral infections in the urinary system of recipients of lung transplants^[97-102]

A small number of cases of BKN in lung transplant

Table 3 BK Nephropathy in heart transplant recipients

Ref.	Gender age	Renal function	Clinical associations
[11]	Male, 65 yr	ESRD Refused dialysis	No rejection episodes Urothelial transitional cell carcinoma causing bilateral hydronephrosis Death following perforated gastric ulcer
[84]	Female 59 yr	SCr 5.0 mg/dL Awaiting dialysis	Three severe rejection episodes early
[85]	Male 57 yr	ESRD On dialysis	Repeated rejection episodes
[86]	Male 26 yr	ESRD On dialysis	Multiple rejection episodes
[89]	Male 54 yr	ESRD Dialysis	Persistent rejection Death from arrhythmia
[90]	Male 12 yr	Last SCr 2.0 mg/dL	Cardiomyopathy from chemotherapy for Ewing's sarcoma One rejection episode
[91]	Male 8 yr	ESRD On dialysis	8 rejection episodes in 1 st heart transplant BK nephropathy after 2 nd heart transplant
[93]	Female 9 yr	Peak SCr 1.9 mg/dL Last SCr 1.2 mg/dL	Rejection episodes not reported Reduction in BK viral load and improvement in renal function after leflunomide was started
[94]	Male 14 yr	ESRD Dialysis	Multiple rejection episodes Lymphoproliferative disorder in the 12 th year BK nephropathy in the 16 th year Death from multiple organ failure
[96]	Male 60 yr	ESRD On peritoneal dialysis	One rejection episode
[96]	Male 43 yr	eGFR 40 mL/min	Recurrent giant cell myocarditis in the transplanted heart One rejection episode

BK nephropathy was usually manifested several years post-heart transplantation. Ages reported in this Table are the calculated ages at the time of diagnosis of BK nephropathy. ESRD: End-stage renal disease; SCr: Serum creatinine; eGFR: Estimated glomerular filtration rate.

recipients has been reported^[98,101,102]. Pertinent features of these patients are summarized in Table 4. Two of the three patients developed ESRD and were started on dialysis. One of these two patients died. One case of nephropathy secondary to a different polyomavirus (simian virus 40 or SV40) in a 32-year-old man with cystic fibrosis who had received a lung transplant was also reported^[97]. This case progressed to ESRD. Another publication reported a case of BK hemorrhagic cystitis in a lung transplant recipient^[99].

Thomas *et al.*^[100] studied longitudinally the frequency of viruria from three different polyomavirus species (BKV, JCV, SV40) in lung transplant recipients. Viruria, at least in one instance, was found for BKV in 42% of the patients, for JCV in 28% and for SV40 in 7%. Although no definitive evidence of clinical polyomavirus infection was detected in this study, patients with viruria had shorter survival.

BK viral infections in the urinary system of recipients of liver transplants^[32,88,103-113]

We found only one reported case of BKN in a liver transplant recipient^[112]. This case is summarized in Table 4. One man with combined liver-kidney transplants developed IgA nephropathy in his native kidneys and BKN in the transplanted kidney^[110].

Several reports analyzed the frequency of BK viruria and viremia and its relationship with renal disease in liver transplant recipients^[32,88,103-109,111,113]. Low frequencies of BK viruria and viremia and low risk of BKN were commonly reported^[32,88,103,108]. Salama *et al.*^[104] concluded that BKV infection is not associated with a decline in renal function in liver transplant recipients. Rauschenfels *et al.*^[105] concluded that hepatotropic viruses, including BKV, do not have a major role in the pathogenesis of biliary atresia, which is the major condition leading to liver transplantation in pediatric populations.

Higher frequencies of BK viruria and viremia and a risk of kidney disease from BKV infection were reported in a few studies of liver transplant patients. Loeches *et al.*^[106] reported BK viruria in 21% and BK viremia in 18% of the liver recipients, the last one early after transplant, and concluded that persistent BK viremia may be associated with renal dysfunction. Demir-Onder *et al.*^[111] reported similar results. Higher frequency of BK viruria in pediatric than adult liver transplant recipients was described by Brinker *et al.*^[107]. Finally, Mitterhoffer *et al.*^[109] reported a higher frequency of BK viremia (56%) in prospective liver transplant recipients with preexisting chronic kidney disease than in those with normal kidney function (14%).

BK viral infections in the urinary system of recipients of pancreas and kidney-pancreas transplants^[114-135]

We found only one confirmed case of BKN in a recipient of an isolated pancreatic transplant recipient^[114]. This case is summarized in Table 4. BKN has been reported in renal transplants of several recipients of combined kidney-pancreas recipients^[115,117-120,123-125,128,129,132-135]. The prevalence of BKV replication and BK viruria in those with combined kidney-pancreas transplants was high in several studies^[116,126-128]. However, one study^[120] reported a low incidence of BKN (2.9%) in recipients of combined kidney-pancreas transplants. CMV viremia may prevent reactivation of BKV in these patients and in recipients of solitary kidney transplants^[130].

Preservation of pancreatic function was reported uniformly in recipients of combined kidney-pancreas transplants with BKV infection^[115,117,119,120,124,128,129,133]. Preservation of normal kidney transplant function was reported in some studies^[129,132-134], while other studies^[117-119,123] concluded that BKN was an important cause of significant deterioration of the transplanted kidney function. A multivariate analysis performed by Heilman *et al.*^[121] identified BKN and a serum creatinine level at or above 1.6 mg/dL as independent correlates of renal graft fibrosis in kidney-pancreas transplant

Table 4 BK nephropathy in recipients of lung, liver and pancreas transplantation

Ref.	Gender age	Renal function	Clinical associations
Lung [98]	Male 40 yr	ESRD On dialysis	Metastatic seminoma treated successfully Three rejection episodes
[101]	Female 72 yr	Peak SCr 2.6 mg/dL Last SCr 2.2 mg/dL	Prolonged neutropenia post-transplant No rejection episodes
[102]	Male 9 yr	ESRD Dialysis	Collecting duct carcinoma Death from respiratory and cardiac failure
Liver [112]	Male 59 yr	SCr 1.9 mg/dL at diagnosis	Multiple rejection episodes Follow-up after diagnosis not reported
Pancreas [114]	Male 54 yr	SCr 2.2 mg/dL At diagnosis	Follow-up after diagnosis not reported

ESRD: End-stage renal disease; SCr: Serum creatinine.

recipients. A recent study by Schachtner *et al.*^[135] concluded that in comparison to recipients of solitary kidney transplants, recipients of combined pancreas-kidney transplants exhibit a higher incidence and severity of BKN.

The diagnosis of BKN in recipients of combined kidney-pancreas transplants is complicated by the potential absence of decoy cells in the urine. Decoy cells are an important diagnostic clue for BKV infection in the urinary tract. High concentrations of pancreatic enzymes in the urine of transplanted patients may degrade these cells^[122]. Quantitative nucleic acid testing for BKV may assist in the diagnosis of BKN in these subjects^[131]. Kubal *et al.*^[125] reported renal transplant nephrectomies and subsequent successful combined kidney-pancreas transplants in two patients who had developed BKN and ESRD in the initial kidney allograft.

In general, BKN in native kidneys of patients with various transplanted organs is substantially less frequent than in transplanted kidneys, but like BKN in transplanted kidneys tends to lead to ESRD and is associated with significant mortality.

BKV INFECTIONS IN OTHER POPULATIONS

BKV infection with various clinical manifestations has been reported more frequently with diagnostic entities either causing immunosuppression or requiring therapeutic immunosuppression than in individuals without an apparent immunosuppressed state. The manifestations of BKV infection in immunosuppressed and non-immunosuppressed states are briefly discussed below.

BKV infections in patients with HIV infection have

been studied extensively^[136-168]. Both BKN^[139,147,151,154,155,159,164,166] and hemorrhagic cystitis^[157,165] have been reported in HIV patients. A series of studies addressed rates of BK viremia and viruria^[136,137,140,141,143,144,162-163,168], the pathogenesis of BKV infection^[157,165] and various clinical aspects of this infection^[138,140,145,146,149,150,152-154,156,158,160,167] in HIV-positive populations.

A patient under treatment for granulomatosis with polyangiitis developed BK hemorrhagic cystitis^[169]. However, in a series of patients with vasculitis associated with ANCA, only those who had received a kidney transplant exhibited BK viremia^[170]. Manifestations of BKV infection in patients with systemic lupus erythematosus (SLE) include viruria and viremia, and the presence of decoy cells in the urine of a patient with BK viruria, hemorrhagic cystitis and hemophagocytic syndrome^[171,172]. The tendency of experimental animals with BKV infection to form anti-double stranded antibodies (anti-dsDNAs) has led to the hypothesis that BKV infection triggers SLE^[171]. Life threatening hemorrhagic cystitis secondary to polyomavirus JC was reported in an adolescent with ataxia-telangiectasia^[173].

BKV infection in patients with various malignancies has been a major focus of the literature^[174-186]. An early study reported BK viruria in patients receiving chemotherapy for malignancy^[174]. BKN has been diagnosed in patients with chronic lymphocytic leukemia^[176,177,180,183], acute lymphocytic leukemia^[178,180,185] and Hodgkin's lymphoma^[175]. BK cystitis was reported in patients with Hodgkin's lymphoma^[182,184,186]. One other patient with lymphoma^[179] developed neurological manifestations of BKV infection.

The potential role of BKV infection in tumorigenesis has received great attention^[187-248]. Urothelial malignancies in association with BKV infection were described in several recipients of kidney transplants^[200,205,213,214,216,220-223,227,229,233,234,236,238,239,245,247] and one heart transplant recipient^[243]. Malignancies in non-transplanted subjects in which BK infection may play a pathogenetic role include bladder carcinoma^[201,211], renal cell carcinoma^[192,230], prostatic carcinoma^[212,217,235,245], Kaposi's sarcoma^[197], neuroblastoma^[199], leukemia, non-Hodgkin's lymphoma^[205], colorectal carcinoma^[215], gastrointestinal B-cell lymphoma^[240], oral squamous cell carcinoma^[244], cervical carcinoma^[224], breast carcinoma^[226] and melanoma^[206].

The role of BKV in tumorigenesis has been disputed. Several studies^[187,203,208,216,223] failed to find an association of BKV infection with various malignancies and published reviews of the role of BKV in malignancies^[202,209,219,231,232,241,247] reflect the current uncertainty about this topic. However, in animal experiments BKV has been shown to play a role in tumorigenesis^[190,191,193,195,196,198] and several reports^[192,194,199,201,204,209,210,217,218,237,242] have addressed pathogenetic pathways potentially linking BKV infection and tumorigenesis. A commonly discussed mechanism is inactivation of the tumor suppressor proteins p53 and pRB

family by the large T antigen T (T-Ag), which is a major antigen of BKV^[199,204]. Other proposed pathways of tumorigenesis include the role of BKV as a cofactor in various malignancies^[217,237] and BKV integration in the human genome^[242].

Finally it is worth noticing that BKV infections with manifestations from the urinary system have been rarely reported in subjects without other systemic diseases. Examples of these infections include a case of BKN, urothelial ulceration and renal pelvic fibrosis with an imaging picture of a renal mass^[249] and the association of BK, and to a greater extent JC, viruria with asymptomatic hematuria in a small sample of Koreans^[250].

CLINICAL MANIFESTATIONS OF BKV INFECTION OTHER THAN NEPHROPATHY OR HEMORRHAGIC CYSTITIS

Table 5 shows clinical manifestations of BKV infection that have been reported so-far. Manifestations other than BKN and hemorrhagic cystitis^[15,78,81,145,146,251-287] will be reviewed in this section. In addition to the kidneys and urinary bladder, BKV was detected at autopsy in the epithelial cells of the ureters of a patient with non-Hodgkin's lymphoma^[15]. Ureteral involvement by BKV with various degrees of urinary obstruction was reported in patients with bone marrow or hematopoietic stem cell transplants^[78,81,252,255] and renal transplants^[251,253,254]. Fatal BK pneumonia was reported in three patients with hematopoietic stem cell transplants^[257,259,260] and two patients under treatment for chronic lymphocytic leukemia^[258,261]. BKV infection also accounted for 8% of the acute respiratory infections in non-immunocompromized children^[256]. BKV infections in non-immunocompromized patients are probably under represented.

Various neurological syndromes associated with BKV infection have been reported in patients with acquired immune deficiency syndrome (AIDS)^[138,142,145,150,152,158,262,269]. In addition to AIDS patients, BK meningoencephalitis has been reported in non-immunocompromized subjects^[263,264], in patients with malignancies including chronic lymphocytic leukemia^[261], Hodgkin's lymphoma^[266], and in a kidney transplant recipient^[273]. Progressive multifocal leukoencephalopathy, also often diagnosed in AIDS patients, has been associated primarily with the JCV^[261,265], but has also been reported in association with BKV infection in one patient^[270]. However, this last association needs confirmation^[271]. A case of progressive multifocal leukoencephalopathy associated with both JC and BKV infections in a non-immunocompromized patient has also been reported^[272]. BK retinitis associated with other manifestations of BKV infection has been reported in AIDS patients^[145,146]. Progressive outer retinal necrosis developed in a kidney transplant recipient with BKV and varicella zoster virus in the vitreous fluid^[275]. This retinal disease was probably caused by varicella zoster virus. Neurological synd-

Table 5 Clinical manifestations of BK virus infection

Uropoietic system
Nephropathy
Hemorrhagic cystitis
Ureteritis - ureteral obstruction
Respiratory system
Upper respiratory infection
Pneumonia
Central nervous system
Meningoencephalitis
Progressive multifocal leukoencephalopathy (probable)
Retinae
Retinitis
Progressive outer retinal necrosis (questionable)
Blood vessels
Vasculitis
Gastrointestinal system
Intestinal ulcers
Lower gastrointestinal bleeding
Hematopoietic system
Pancytopenia
Neutropenia
Hemophagocytic syndrome
Polyclonal gammopathy
Malignancies
Urothelial tumors
Various other tumors

romes associated with BKV infection were analyzed in two reviews^[268,274].

Deltoid muscle biopsy in a renal transplant recipient who developed progressive weakness and dyspnea, and died after several episodes of life-threatening arrhythmias revealed BK vasculitis^[276]. A detailed description of the glomerular histologic changes in a large study of renal biopsy samples with BKN^[277] failed to identify vascular changes. However, in other reports BKV was found to be localized in endothelial cells of both renal arteries and venules^[278] and venous thrombosis associated with BKN was diagnosed in a renal allograft by ¹¹¹In leukocyte imaging^[279].

BKV is replicating in salivary glands^[280]. High frequency of BKV shedding from the gastrointestinal tract in recipients of hematopoietic stem cell transplants has been reported^[65]. Gastrointestinal bleeding associated with bowel lesions putatively caused by BKV infection was reported in a renal transplant recipient^[281] and a hematopoietic stem cell transplant recipient^[282]. Interestingly, high rates of BK viruria in patients with inflammatory bowel disease have been documented^[283]. However, the clinical significance of this finding will require further study.

Pancytopenia or severe neutropenia associated with BKV infection have been found in kidney transplant recipients^[284-286]. Hemophagocytic syndrome was diagnosed in one of these patients^[286]. Polyclonal gammopathy triggered by BKV infection was reported in a hematopoietic stem cell transplant recipient suffering from B-cell lymphoblastic leukemia^[287]. BKV DNA has been isolated in normal hepatic tissue and elevated hepatic enzymes were reported in bone marrow trans-

plant recipients who had BK viruria^[24].

Key points of part A

Clinical manifestations of BKV infection have been reported in patients with various immunosuppressed states and small numbers of subjects with apparent absence of immunosuppression. Although BKN is much less frequent in the native kidneys of organ transplant recipients than in transplanted kidneys, it is uniformly associated with poor outcomes. BKV infection causes a variety of clinical manifestations in addition to nephropathy and hemorrhagic cystitis.

PART B DIAGNOSIS OF BKN AND PATHOGENESIS OF BKV INFECTION

DIAGNOSIS OF BKN^[10,13,14,16,22,277,288-336]

BKN accounts only for a small fraction of the renal dysfunction encountered in transplant recipients. Its diagnostic features have been extensively studied in renal transplant recipients. Risk factors for the development of BKN including certain immunosuppressive agents, such as mycophenolate, and manifestations of BKV infection in the urinary tract, including BKN, ureteral obstruction, lymphocele, bacterial urinary tract infection, hematuria, and elevated serum creatinine levels have been studied in renal transplant populations^[22,288]. A study from South Korea^[336] identified an accompanying acute rejection episode, in addition to advanced histologic stage of BKN and elevated serum creatinine levels, as factors increasing the risk of renal transplant failure in renal transplant recipients. Reports involving renal transplant recipients constitute the main source of information reviewed in this section.

Renal biopsy constitutes the gold standard for the diagnosis of BKN. Various aspects of the renal biopsy in BKN have been studied^[10,13,14,16,291,294,296,298,299,301-303,307,311,312,314,316,322,324,328]. An early report by Rosen *et al.*^[13] identified tubulo-interstitial nephritis as the main histologic picture of BKN. Viral replication in the tubular epithelial cells, starting in the renal medulla and extended later to the renal cortex, initiates cytopathic changes in the renal tubules that can be confirmed by immunohistochemistry, *in situ* hybridization, electron microscopy or polymerase chain reaction (PCR)^[291,316].

The Maryland classification of BKN^[291,296,298], which is based on the degree of interstitial inflammation and fibrosis, schematically recognizes three histological patterns which are considered to represent successive stages of BKN. The first pattern is characterized by absent or minimal interstitial inflammation and the presence of viral cytopathic changes, including karyomegaly, hyperchromasia, and basophilic nuclear inclusions, in a few tubular cells located primarily in the renal medulla. Cytolytic changes, including cell necrosis, apoptosis, smudged chromatin and hobnail nuclei with desquamation into the tubular lumen and formation of necrotic casts accompany often the cytopathic

changes^[291].

The second pattern of the Maryland classification is characterized by focal or diffuse clusters of tubules with cytopathic and cytosolic changes plus interstitial collections of inflammatory cells, primarily lymphocytes, with tubulitis and tubulo-interstitial atrophy in some cases. The third pattern is characterized by extensive interstitial fibrosis and tubular atrophy, lymphocytic infiltration and paucity of viral cytopathic changes. The course of renal dysfunction roughly correlates with the histological staging^[291].

A key diagnostic feature of BKN is the finding of viral cytopathic changes, which are apparently identical for papovaviruses BKV, JCV and SV40^[296]. The nuclei of the infected cells are large and contain a basophilic inclusion that either replaces the chromatin or displaces it to the periphery of the nucleus (Figure 1A and C). The presence of a halo around the BKV inclusion is used to differentiate between BKV infection and CMV infection. The BKV infected cells have larger nuclei in comparison to cytoplasm and no viral inclusions in their cytoplasm. Immunohistochemical staining for SV40 large T antigen (Figure 1B), which cross-reacts with BKV and JCV, identifies the presence of a papovavirus and allows its differentiation from adenovirus, which can also cause nephritis with intranuclear viral inclusions morphologically identical to those of papovaviruses. Transmission electron microscopy of cells infected with papovavirus shows characteristic intranuclear deposits of polyhedral virions with an average diameter of 40 nm and in some cases fibrillary or microtubular inclusions. Electron microscopy may assist in the differentiation of papovavirus virions from those of CMV, adenovirus and herpesvirus^[296].

The proposed sequence of events leading to the histological changes of BKN is as follows^[296]: Viral infection leads to cell death and disintegration with discharge of virions in the extracellular space. Entrance of virions into adjacent cells leads to spread of the infection. Infected renal tubular cells and virions exfoliate in the urine. If the tubular injury is severe, tubular basement membranes rupture causing spillage of virions and viral proteins into the blood stream. Severe tubular injury also causes an inflammatory response with influx of tubulo-interstitial B cells, T cells, plasma cells and macrophages (Figure 1C). This histological picture can be confused with acute cellular rejection (ACR) in renal transplant recipients. When it is severe or persistent, the tubular injury leads to tubular atrophy and interstitial fibrosis.

The utility of the Maryland staging of BKN, modified by the American Society of Transplantation, has been successfully tested in clinical practice. In one study, the third pattern was associated with higher serum creatinine levels at presentation and greater renal function deterioration in follow-up measurements than the first or second pattern^[299].

The histology of BKN has been reviewed in successive Banff group meetings^[307,312,314,328]. The original

Banff classification also recognizes three histologic patterns, characteristic of the stages of BKN: (1) an early stage without tubular cell necrosis; (2) a stage of active BKN with tubular cell necrosis (Figure 1A); and (3) a late stage characterized by fibrosis (Figure 1D)^[307]. In one study, reasonable agreement between various nephropathologists was reported using this Banff classification^[312]. However, another study failed to demonstrate superiority of the Banff staging of BKN over the Maryland classification^[314]. The latest Banff group meeting stressed the need for improving the reproducibility of large SV40 T antigen immunostaining, which is proposed as an index of the BKV viral load and a potential predictor of the renal graft outcome in patients with BKN^[328]. *In situ* hybridization may offer an alternative to immunohistochemistry in the diagnosis of BKN^[316]. The diagnostic challenges associated with BKN were recently reviewed by Masutani^[324].

In renal transplant biopsies with BKN, the presence of peritubular capillary staining for C4d raises the possibility of coexisting antibody-mediated (humoral) rejection. Some biopsies with BKN show staining of tubular basement membranes for C4d, and this finding is correlated with marked viral cytopathic effect^[303]. Granular immune complex deposits in the tubular basement membranes^[301] and in the subepithelial space of glomerular basement membranes^[302] have been described in patients with BKN. In the latter, BKV was identified ultrastructurally in the immune deposits^[302]. Glomerulonephritis attributed to BKV infection was found in a few renal transplant recipients^[277,321].

The focal lesions of the early stages of BKN may be missed in a renal biopsy^[298,324]. Several diagnostic pathways complementing the renal biopsy have been explored. The value of surveillance renal biopsies in early diagnosis of BKN has been discussed in several reports^[22,310,313]. BK viruria^[22,297,306,308,317,322,332,334] and viremia^[22,289,308,309,317,322,323,332,335] provide another tool for the detection of BKN. High levels of viruria or viremia correlate reasonably with the presence of BKN. Cut-off levels for the diagnosis of BKN have been proposed and tested.

Detection in urinary samples of desquamated tubular or urothelial cells with BKV inclusions provide another tool for the diagnosis of BKV infection in the urinary system^[291]. The cardinal features of these cells, known as "decoy cells", because of their similarity to malignant cells, in a Papanicolaou stain include a greatly enlarged nucleus with a basophilic inclusion next to the chromatin producing a ground-glass or gelatinous look. A halo may surround the basophilic inclusion. Decoy cells may also be detected by phase-contrast microscopy^[292]. Decoy cells led to the diagnosis of BKV infection in an immunocompetent child with otitis media followed by dysuria^[315]. However, decoy cells may be absent from the urine of patients with documented BKN^[333]. In one study, the positive predictive value of decoy cells was low, but improved by immunohistochemical staining of the urine for SV40 large T antigen^[331]. Negative-stain electron

microscopy and semi-quantitative identification of free BKV particles in the urine assists in the identification of patients at high risk of BKN^[300]. Genotyping of BKV by an improved PCR method^[327] and serologic tests^[329] may help in the diagnosis of BKV infection. Ultrasonographic pictures suggesting BKN were recently reported^[330].

In renal transplant recipients, the differentiation between ACR and BKN presents difficulties^[294]. The histologic picture of tubulo-interstitial nephritis is indistinguishable between the two conditions^[319]. Immunophenotyping of the mononuclear cells in the interstitial infiltrates was found to be promising in some studies^[304,318], but could not differentiate between ACR and BKN in others^[305]. Serial monitoring of donor-specific cell-free DNA in the urine may be a sensitive biomarker of acute kidney injury, but does not allow the distinction between ACR and BKN^[320]. Urine analysis methodologies potentially allowing the differentiation of these two conditions are proteomics^[325] and characterization of the percentages and absolute numbers of CD4(+) and CD8(+) effector memory T cells^[326].

Several other questions related to the diagnosis of BK infection in the urinary tract have been investigated. Immunohistochemical analysis of renal biopsies revealed differences in the inflammatory infiltrate between different BKV strains^[290]. Additionally, latent BKV and JCV were found in the urinary tract of immunocompetent subjects in an autopsy study^[295]. One review^[311] analyzed the diagnosis and pathogenesis of BK cystitis in hematopoietic cell transplant recipients. Another study found a high rate of mutations in the coding region VP-1 of BKV in HIV-infected patients with low CD4(+) counts^[330]. The authors of this study postulated that these mutations could affect the clinical manifestations of BKV infection in HIV patients. Whether the diagnosis of BKV infection will require in the future an analysis of the mutations of the virus in various patient groups or individual patients is not clear.

PATHOGENESIS OF BKV

INFECTION^[10,20,35,126,336-436]

BKV is a small, unenveloped icosahedral DNA virus. Its genome sequence contains three functional regions. The early region encodes the large T antigen (T-Ag) and the small T antigen. These antigens are involved in BKV DNA replication and could be treatment targets. As noted earlier, interaction of T-Ag with p53 is believed to be the main pathway of tumorigenesis by BKV. The late region is responsible for the production of the proteins VP1, VP2 and VP3, the role of which in BKV infection will be examined later. Finally, the non-coding control region controls the expression of the viral genes^[423].

The pathogenesis of BKV infection, and specifically of BKN, is a complex process that has not been elucidated completely. Costa *et al.*^[10] listed factors related to the patients, the transplanted organs, and the BKV genotypes as determinants of the development

of BKN. The first contact with BKV occurs early in childhood. Antibodies against BKV are found in 50% of the subjects by age 3 and in 80%-90% by age 20 years, with decrease in the antibody titers in older age^[20]. The incidence of primary infection is similar in immunosuppressed and non-immunosuppressed children^[340].

Age older than 50 years is one of the patient-related risk factors for BKN^[10]. In non-immunocompromised subjects, the rate of BK viruria is low below the age of 30 years and increases progressively after that age^[35]. Older subjects excrete preferentially the BKV viral subtypes I and IV^[35]. In a fraction of the subjects the virus persists without clinical manifestations, but in a state of active asymptomatic replication^[35]. Organs harboring replicating BKV include the kidneys, the bone marrow and the brain^[35]. Persistence of the virus in other tissues, including spleen, normal thyroid glands^[429], pancreas^[342], and lymphocytes in HIV-positive patients^[344], has also been reported. Active BKV disease in various organs is more frequent if another insult to these organs has also occurred. Examples of this sequence include the relatively high frequencies of BKN in kidney transplant recipients and hemorrhagic cystitis in bone marrow or stem cell transplant recipients.

The mode of BKV transmission is not completely understood. Transplacental transmission was described in an early study^[337]. Transmission through the transplanted kidneys has also been documented^[351,430]. Replication of BKV in salivary glands was found *in vitro* suggesting oral transmission^[367]. After the primary infection the virus remains latent in host tissues and is reactivated when an immunosuppressed state supervenes. Following renal transplantation, reactivation of BKV demonstrated by BK viruria is usually noticed after 3-6 mo while reactivation of JCV occurs as early as five days post transplantation^[379]. Early BKV reactivation is associated with viremia^[377] and worse transplant function^[372].

Circulating BKV is taken up by cells. In experimental animals, endothelial cells in hepatic sinusoids and in the kidney were shown to remove rapidly blood-borne BK and JCV-like particles^[409]. Upon contact with the cell membrane BKV is bound to membrane receptors^[381]. The identified specific BKV receptors include polysialated ganglioside GT1b and (2,3)N-linked sialic acid^[351]. Cellular entry of BKV is through caveolar endocytosis^[357,369]. The GT1b receptor, which is involved in caveolar endocytosis^[351], could provide a treatment target in the future.

Differences in cellular entry and trafficking exist between various cell types and viral genotypes^[392]. The capsid proteins VP2 and VP3 have important roles in the nuclear entry of BKV^[414]. BKV genotypes have different potential for pathogenicity^[147,351,356,368,380,389]. The family of transforming-growth factors (TNF) plays a role in BKV gene expression^[359]. BKV infection activates the TNF receptor system in BKN^[432,433]. Monocyte and Th-2 cytokines, including IL-1 RA, IL-3, IL-6 and sIL-6R are

elevated in the urine of renal transplant recipients with BK viruria and may be involved in the pathogenesis of BKN^[370]. In general, BKV infection of renal tubular epithelial cells leads to activation of cellular genes involved in cell cycle regulation and apoptosis and downregulation of a small number of genes^[373].

After entry into the cytoplasm, BKV is transported into the endoplasmic reticulum along the microtubules by a complex mechanism favored by acidic environment^[368]. The ER associated degradation (ERAD) pathway, which is responsible for the transfer to the cytosol of ER secretory proteins that have not attained their proper conformation, where they are degraded by proteasomes, is responsible for transferring BKV into the cytosol, followed by entry of these proteins into the nucleus^[372]. After entry of BKV into the nucleus, BKV genome release takes place^[383]. The Derlin family of the ERAD translocation complex proteins is important for the trafficking of BKV and other polyomaviruses^[370]. Proteasome action is also important in BKV trafficking^[392].

Several reviews have stressed the role of innate immunity in the pathogenesis of BKV infection and the need to monitor both the BK viral load and the state of immunity in populations prone to BKV infection as the first step in the timely management of this infection^[351,395,406]. A recent report reviewed potential preventive and therapeutic approaches for BKV infection related to the mechanisms of innate immunity^[433]. Innate immunity compounds that inhibit BKV infection include lactoferrin^[349], the antimicrobial defensins alpha-defensin human neutrophil protein 1 (HNP1) and human alpha-defensin 5 (HD5) which were shown *in vitro* to aggregate BKV virions thus blocking cellular entry^[363], and the cellular DNA damage response (DDR) which modulates BKV replication^[388,431]. Human leukocyte antigens (HLAs) that are associated with lower risk of BKV infection include HLA-A2, HLA-B44, HLA-DR5^[397] and HLA cw7^[421]. Expression in BKV-infected cells of p53, binding of which to the BKV large T-Ag is proposed as a mechanism of tumorigenesis, may provide a therapeutic target in the future^[353]. In renal tissues, large T-Ag is expressed in decreasing frequency in medullary collecting ducts, distal and proximal convoluted tubules and Bowman's capsule^[350]. Viral replication pathways which could form the basis of therapeutic approaches in the future include agnoprotein, a viral phospho-protein^[364], viral microRNA (miRNA)^[394,410], and autophagy in host cells^[401].

Disruption of adaptive immunity plays a major role in the pathogenesis of BKV infection. Both cellular and humoral aspects of adaptive immunity in BKV infection have been extensively studied. Age affects both the cellular and humoral immune responses to BKV infection^[407]. BKV-specific cellular immunity is vital for control of viral replication and prevention of chronic viral disease^[383]. Low levels of cytotoxic T cell (CTL) response correlate with high BKV loads and high anti-BKV antibody titers, while a high CTL response correlates with low viral loads and low anti-BKV

antibody titers^[347]. The finding that viral capsid epitopes of BKV share homology with other polyomaviruses, including JCV and SV40 suggests that infection with one of the viruses could establish cross-immunity against the other viruses *via* a cellular-immune response^[348].

Loss of BKV-specific T cell immunity in the post-transplant period identifies kidney transplant recipients at high risk for BKV infection^[427]. In patients with BKV infection, recovery of cellular immune responses to large T-Ag correlates with improvement of BKN^[365,384]. However, in one study the percent of activated T cells correlated with the degree of BK viremia^[396]. In the same study, patients with decreased renal function exhibited high levels of activated T cells and BK viremia.

Monitoring of both non-virus specific and virus-specific T cell responses in transplant patients has been advocated^[405,417]. Monitoring these responses post-transplantation may have a role in the detection of BKV reactivation^[423]. T cells respond to different BKV antigens^[419]. The nuclear factor of activated T cells (NFAT) binds to the viral promoter and regulates viral transcription. This factor is involved in a complex regulatory pathway that can affect the course of BKV infection^[375]. The genetic variation of BKV strains is limited^[425]. In HLA-A*0201 individuals, cytotoxic T-cell lymphocyte (CTL) responses are elicited towards two of the VP1 epitopes, VP1(p44) and VP1(p108)^[347]. CTLs directed against VP1(p44) are more abundant than VP1(p108) in healthy individuals, while the opposite is true in kidney transplant patients who present with BKN. This suggests a shift in the epitope immunodominance in the setting of active BKV infection^[347]. Flow-cytometry analysis of BKV-specific T cells also showed that VP3 is an important target of cellular immunity^[386].

CD4 T cells have a role in BKV clearance^[387,412]. Though the pattern of cellular response to BKV antigens has not been fully clarified, it has been discovered that in kidney allograft recipients, VP1-specific interferon-gamma producing T cells were more likely to be CD4⁺, while CD8⁺ lymphocytes are more frequently directed against the large T antigen^[361]. Stimulation of CD28 in T cells is one of the rejection mechanisms blocked by belatacept. Subpopulations of human T cells exposed to antigens may be activated by mechanisms different than CD28 and cause rejection resistant to belatacept. In mice models polyomavirus exposure leads to reduced expression of CD28 in T cells and was proposed as a mechanism of resistant rejection^[422]. Activated CD4 T cells upregulate CD30, another cell marker of B and T cells, causing an increase in serum soluble CD30 (sCD30), which plays a role in the pathogenesis of rejection^[366]. Levels of sCD30 are associated with BK viremia and may be of use in the management of the immunosuppressive regimen for renal transplant patients as well as a prognostic factor for graft rejection^[436].

The role of dendritic cells in antigen presentation to T cells is well known. Dendritic cell deficiency was shown to be a risk factor for reactivation of BKV infection after renal transplantation^[382]. A genotypic analysis in renal

transplant recipients found that low frequencies of the activating receptor KIR3DS1 are associated with the development of BKV infection and that there appears to be a genetic predisposition for BKN linked to natural killer cells^[402].

The interplay between genetics and immunology is reflected in the finding that the NFAT can transcriptionally regulate BKV. During T-cell activation, NFAT translocates to the nucleus where it regulates the expression of various genes^[341]. NFAT regulates BKV transcription, while NFAT inhibition with an NFAT inhibitor peptide, 11R-VIVIT, reduces BKV replication^[375]. In addition there is growing evidence that epigenetic factors may contribute to the regulation of BKV and its tissue propagation. Viral microRNAs (miRNAs) are playing a crucial role in viral replication. BKV-encoded miRNAs (miR-B1) have been studied in patients with BKN. After BKV infection, miR-B1 levels are significantly increased and these miRNAs suppress T-ag-mediated autoregulation of BKV replication. Thus, miR-B1 offers a potential treatment strategy for controlling BKV infection^[410].

In addition to cellular immune response, humoral immunity also plays an important role in BKV infection. Antibodies to various BKV antigens were detected in normal controls and patients suffering from various diseases; patients with urinary bladder carcinoma exhibited the highest frequency and titers of anti-BKV antibodies^[338]. HIV patients with BK viremia and JC viremia have a low frequency of antibodies against these two viruses^[343]. In renal transplant recipients, BKV-specific IgG levels were in the pre-transplant period lower in those who developed active BKV infection than in those who did not develop BKV infection; the rise in the antibody titers post-transplant, however, was higher in patients who developed BKV infection^[360]. In this last group, antibody titers correlated with the intensity of BKV infection. This suggested that specific antiBKV IgG response is not associated with viral clearance^[360]. A prospective study concluded that determination of the serostatus of prospective kidney transplants and recipients allows stratification of the risk for BKV infection post-transplant^[398].

Pre-kidney transplant levels of anti-BKV antibodies did not clearly predict post-transplant BK viremia in pediatric renal transplant recipients^[374]. However, there is considerable evidence pointing to a link between antibody titers and BKV disease progression in the post-transplant period. Pediatric patients with hemagglutination-inhibition titers < 40 were found to be at greater risk of disease progression, and seronegative recipients were found to be at greater risk of developing BKN if seronegativity was demonstrated by the VP1 enzyme immunoassay^[351]. In patients at different stages of BKN, BKV-specific IgG levels were higher in those who had recovered from BKN than in patients with acute infection. Interestingly, the density of plasma cells in the interstitial infiltrates of BKN was found to correlate with the levels of circulating anti-BKV IgM

in one study^[378]. BKV infection was fatal in a patient with hyper-IgM deficiency. This patient, whose class switching from IgM to IgG was impaired, was not able to produce the protective IgG antibodies against the virus^[351]. This case suggests that immunoglobulin response has an important role in controlling BKV infection.

Measurement of the anti-BKV titers is an important tool to detect the onset of viral replication^[352]. Further research is needed to determine the extent to which these antibodies can neutralize the virus or its active viral components, though some suggest that there are BKV neutralizing antibodies that target VP1^[351,361,378]. *In vitro* coinubation of BKV with human intravenous IgG preparations caused 90% inhibition of viral DNA after 7 d in culture, a finding consistent with a direct neutralizing mechanism. This suggests a mechanism of protection against viral reactivation in an immunocompetent person by virus-specific antibodies^[378].

Other aspects of antibody formation in BKV infection are of importance. In experimental animals, BKV infection induces the formation of anti-double stranded DNA antibodies^[362]. This finding has led to the suggestion that BKV is implicated in the pathogenesis of SLE, as noted earlier in this report^[171,172]. In a recent report, preemptive reduction of immunosuppression for BK viremia was found to be associated with high incidence of formation of HLA-specific antibodies (dnDSA)^[420]. The authors of this report proposed that in order to prevent the consequences of rejection dnDSA levels should be monitored in renal transplant recipients subjected to reduction of immunosuppression for BK viremia.

The effects of interferon on BKV infection have also attracted attention. Exposure of interferon-sensitive cells infected with BKV to high concentrations of interferon resulted in significant reduction of the BKV load in an early study^[339]. However administration of interferon to a renal transplant recipient with BK viremia and viruria had no appreciable effect in the same study. *In vitro*, interferon- γ inhibits the expression of the BKV T-ag and VP1^[353]. Polymorphisms in the interferon- γ gene appear to affect the development of BKV infection in Hispanics^[408].

A review of subversion mechanisms of several viruses causing kidney disease^[354] stressed the role of immunosuppressed state in the pathogenesis of the viral kidney diseases, included BKN. The state of immunosuppression is the major mechanism of BKV reactivation and has been stressed in numerous reports^[10,351,372,393,422]. Immunosuppressive medications that may increase the risk of BKV infection include tacrolimus^[372,393,403], and mycophenolate^[393]. ABO incompatible kidney transplantation is a risk factor for BKV infection^[413,415]. Although immunoglobulin preparations inhibited BKV replication *in vitro*^[378] and administration of intravenous immunoglobulin was found to be effective and safe in treating BK viremia in one study^[385], desensitization of ABO and HLA incompatible kidney transplant

recipients with IVIG and rituximab was associated with higher incidence of BKV infection^[126,391].

Other factors associated with increased risks for BKV infection and BKN include recipient age exceeding 50 years^[10], male gender, comorbidities (diabetes mellitus)^[10], negative recipient BKV serology prior to transplantation^[10], prior rejection episodes^[10,424], renal dysfunction^[10], large BKV loads^[10], deceased donor^[403], positive CMV serology in donor and recipient^[424], more than one transplant^[424] and hypoxia^[428]. In allogeneic stem cell transplant recipients, severe graft vs host reaction and oral mucositis are risk factors for BKV reactivation^[434]. Mathematical modeling of the immune responses to BKV infection^[432] could provide in the future new developments in the prevention and management of this disease.

Key points of part B

Renal biopsy is required for confirmation of the diagnosis and staging of BKN; BK viral loads in blood and urine and the presence of decoy cells in the use assist in the diagnosis of BKV replication; elucidation of the mechanism of BKV entry into cells and nuclei, factors affecting BKV replication and of the roles of cellular and humoral immunity in KBV infection have the potential of leading to novel prevention and treatment strategies.

PART C TREATMENT OF BKV INFECTION AND DISEASES CAUSED BY OTHER PAPOVAVIRUSES. TREATMENT AND PREVENTION OF BKV INFECTION^[10,19,20,79,92,385,437-493]

Current practices in the prevention and management of BKV infection are based on information obtained primarily from renal transplant recipients. In this patient group, reduction in immune responses to infection as a result of immunosuppression has been recognized as the universal risk factor for symptomatic BKV infection^[10]. A large retrospective study of treatment of BKN in United States renal transplant recipients concluded that the incidence of BKN has been on the rise and is associated with increased risk of graft loss^[19]. The same study reported that certain antirejection medications, including rabbit antithymocytic globulin and tacrolimus/mycophenolate combination, are risk factors for BKN.

Reducing the total immunosuppressive dose and converting to medications less prone to be associated with BKV infection has been reported to have beneficial effects on BK viremia and viruria in various renal transplant cohorts^[447,451,455,471,480,481,484]. In a study from China, monitoring renal transplant recipients for BK viremia and preemptive reduction of immunosuppression was associated with resolution of the viremia and good graft function over five years of follow-up^[481]. Reduction of

immunosuppression, with careful monitoring for signs of rejection of the transplanted organ, and discontinuation of immunosuppressives that are associated with higher risk of BKV infection, *e.g.*, mycophenolate, is currently the mainstay of management of BKV infection in transplant recipients.

Prevention and management of BKV infection in vulnerable populations is hampered by the absence of medications specific for papovaviruses. Certain drug classes have demonstrated antiviral properties *in vitro* and have been tried for preventing or treating BKV infection. The antiviral activity of cidofovir, an acyclic nucleoside phosphonate nucleotide analog, is linked to inhibition of viral DNA polymerases. The drug, which is approved for the treatment of CMV retinitis, was found to inhibit *in vitro* BKV replication in human cell series^[439,483], although one study found modest antiviral activity and low selectivity of this compound^[445]. Beneficial effects of cidofovir in transplant recipients with BKV infections, including BKN and hemorrhagic cystitis, have been reported in case reports and case series^[438,443,446,473].

Cidofovir is administered parenterally. A review concluded that intravesicular administration of cidofovir is effective in cases of severe hemorrhagic BK cystitis^[461]. The use of cidofovir in the management or prevention of BKN is limited by nephrotoxicity, which is the main adverse effect of the drug. Mitochondrial changes in renal tubular epithelial cells^[458] and renal dysfunction may develop in patients receiving the drug. Hydration prior to the injection and concomitant administration of probenecid reduce the risk of nephrotoxicity. Reduction of the dose of cidofovir without probenecid administration was reported to have beneficial effects on the renal function of a patient with BKN^[443]. However, renal dysfunction has led to the discontinuation of the medication in several reports.

The issues raised by cidofovir have led to the search for compounds related to it, but with less toxicity and higher selectivity. A systematic *in vitro* study found several acyclic nucleoside phosphonates, including cidofovir, with inhibitory activity on BKV replication^[459]. Brincidofovir, a compound derived by conjugating cidofovir with a lipid and designed to lead to intracellular release of cidofovir, has antiviral activities against several DNA viruses and was shown *in vitro* to inhibit BKV replication in human urothelial cells^[489]. This compound was recently reported to reduce the viremia and stabilize the renal function without reduction of immunosuppression, which included mycophenolate, in a recipient of allogeneic hematopoietic stem cell transplant with BKN^[79]. Despite the stabilization of the renal function, this patient, who had graft vs host disease, died from sepsis six months after the initiation of brincidofovir treatment. Treatment of BKV infection by brincidofovir will need further evaluation.

Leflunomide is a pyrimidine synthesis inhibitor used in the treatment of rheumatoid arthritis and has been shown to inhibit BKV replication *in vitro* in human

tubular epithelial cells^[452] and human salivary gland cells^[483]. However, only modest antiviral activity and low selectivity of the drug were found in one *in vitro* study^[439], while no antiviral activity of the compound was found in another *in vitro* study^[459]. In case reports and case series, beneficial effects of leflunomide were reported for BK viremia^[93,478], BKN^[442,444,448] and hemorrhagic cystitis^[465] in organ transplant recipients. In resistant cases, administration of cidofovir concomitantly with leflunomide^[442] or ciprofloxacin followed by leflunomide^[478] had apparent beneficial effects. The side effects of leflunomide include hepatotoxicity and neutropenia. Leflunomide treatment requires monitoring of its active metabolite in the blood to ensure therapeutic levels as well as monitoring of hepatic function tests and hematological parameters. A systematic review did not find any kidney transplant survival benefit by the use of leflunomide or cidofovir^[455]. The need for prospective randomized studies was stressed even in studies reporting beneficial effects of leflunomide^[465].

Fluoroquinolones inhibit *in vitro* the DNA topoisomerase of BKV. Levofloxacin and ofloxacin were reported to inhibit BKV replication in human renal tubular epithelial cells *in vitro*^[457]. This effect of this class of antibiotics was criticized because of its low selectivity index^[441]. Ciprofloxacin failed to inhibit BKV replication in another *in vitro* study^[483]. Two retrospective studies in renal transplant recipients reported beneficial effects of fluoroquinolones on BKV infection. Reduction of BK viremia followed ciprofloxacin or levofloxacin administration in one study^[440] and sequential treatment with ciprofloxacin and leflunomide in another study^[478]. However, one retrospective study failed to show any benefit of ciprofloxacin or levofloxacin in the prevention of BKV infection in recipients of allogeneic hematopoietic stem cell transplants^[469] and two randomized studies failed to show any effectiveness of levofloxacin in the prevention of BKV infection^[472] or the treatment of BK viremia^[474] in kidney transplant recipients.

HMG-CoA reductase inhibitors are another class of drugs that has been tried unsuccessfully for the treatment of BKV infection. After the original *in vitro* observation that pravastatin blocks BKV cellular entry^[449], a retrospective multicenter study failed to show any effect of statin doses that maximize their cholesterol-lowering effect on BK viruria or the development of BKN in renal transplant recipients^[479]. Intravenous (*i.v.*) immunoglobulin administration without reduction of the immunosuppression had beneficial effect in a pediatric case of BKN^[450] and, in association with reduction of the immunosuppression, was associated with clearing of the BK viremia and good graft survival in a retrospective study of renal transplant recipients^[385]. Issues associated with IVIG treatment were discussed in the section on pathogenesis. Following immunoglobulin infusion one kidney transplant recipient developed increase in BK viremia and BKN^[464] and a second kidney transplant recipient with BKN developed severe antibody-mediated rejection^[468]. A retrospective study found no difference in

1-year renal transplant outcomes between patients with BKN treated with reduction of the immunosuppression alone or with active treatment including administration of IVIG, leflunomide and ciprofloxacin^[471]. Plasma exchange, along with intravenous immunoglobulin and cidofovir, has also been used for the treatment of BKV infection in renal transplant recipients^[455]. A recent review concluded that reduction of the immunosuppression is the only proven effective treatment of BKN in renal transplant recipients, while cidofovir, leflunomide, fluoroquinolones and *i.v.* immunoglobulin have not been shown to offer any benefits^[480].

The search for immunosuppressive agents lowering the risk of BKV infection has been the topic of several studies. Induction by alemtuzimab was associated with a higher risk of severe rejection and BKN than induction by antithymocytic globulin^[487], even though antithymocytic globulin has been recognized as a risk factor for BKN^[19]. Beneficial effects on BKV infection were reported with the use of the mTOR inhibitors everolimus^[486,493], or sirolimus^[488] instead of mycophenolate and tacrolimus in transplant recipients.

One report reviewed the conservative and surgical approaches to BK hemorrhagic cystitis in bone marrow transplant recipients^[437]. Hyperhydration is sufficient for mild cases. Severe cases may require blood transfusions, suprapubic catheters, permanent bladder irrigation, or various surgical procedures^[437]. Limited experience exists with certain other treatments. Successful combined kidney-liver transplant was reported in a patient with high grade BK viremia, fulminant hepatic failure and loss of his first kidney transplant to BKN^[482]. The first kidney transplant was not removed in this case. Administration of the protease inhibitor bortezomib, which is used as a chemotherapeutic agent in multiple myeloma and mantle cell lymphoma, to a patient with severe BKN and plasma cell-rich infiltrates in the renal interstitium was associated with substantial improvement of the renal function and renal histology^[491]. Treatment by hyperbaric oxygen was associated with resolution of the hematuria in 94% of a series of patients with BK hemorrhagic cystitis^[462].

In a survey of European transplant centers, 66% of the responders stressed the need for new antiviral agents for BKV infection^[485]. Agents that have been tested with some promise in experimental animals or *in vitro* include cyclosporine A^[456], gamma interferon^[460], two inhibitors of the ATPase of the large T BKV antigen, bithionol and hexachlorophene^[463], the small molecule Retro-2(cycl) which inhibits host retrograde viral trafficking^[470], an expression plasmid for the Large BKV T antigen shRNA delivered by virus-like particles^[475], gallic acid-based compounds^[476] and the anti-malarial artesunate^[477]. In a retrospective study in renal transplant recipients with BK viremia, switching the immunosuppressive regime to a combination of low-dose cyclosporine plus an mTOR inhibitor was well tolerated and was associated with better short-term graft function

than reduction of the immunosuppression alone^[466].

The management of BKV infection in transplant recipients is currently based on reduction of the immunosuppression and, in some cases, substitution of mTOR inhibitors for mycophenolate and calcineurin inhibitors. The induction scheme that is best for prevention of BKV infection is not known. Systematic surveillance for BK viremia and viruria^[335,400,451,492] will assist in the early detection and could benefit the outcome of BKV infections.

HUMAN DISEASE ASSOCIATED WITH OTHER PAPOVAVIRUSES^[2-4,12,27,28,97,107,177,250,262,266,342,344,494-502]

BKV belongs to the *Polyomaviridae* family of viruses. Similar structure and animal species as natural hosts are the common features of the members of this family. Other human viruses in the same family that have been associated with human disease include the JCV, the Merkel virus and, probably, the SV40. The natural hosts of SV40 are monkeys and its role in human disease is disputed. The role of *Polyomaviridae* in human disease has been reviewed in several reports^[2-4].

The structure of JCV has the closest association with BKV among all the known human *Polyomaviridae*. A 75% sequence homology between BKV and JCV has been found^[500]. JCV infection has been studied extensively. Substantial rates of JC viremia, viruria and persistence in tissues of transplant recipients and other populations, including non-immunosuppressed subjects, have been reported^[12,27,28,107,343,345,494,495,499,501]. Renal manifestations associated with JCV infection include a case of nephropathy in a patient with malignancy^[177] and decreased renal function in kidney and liver transplant recipients with JC viruria^[497]. The pathogenetic role of JCV in HIV-positive patients with progressive multifocal leukoencephalopathy has been established^[261,265]. JCV is oncogenic in animal species, including primates. In humans JCV infection has been associated with brain tumors and carcinomas of the gastrointestinal tract, breast and cervix, but this association has not been found universally^[496].

Merkel virus is oncogenic in humans. It is linked to Merkel carcinoma, a rare aggressive skin tumor affecting primarily older individuals^[498,499]. Nephropathy associated with SV40 infection was reported in a lung transplant recipient^[97].

The number of *Polyomaviridae* diseases attributed to this viral family is expanding. A recent revision of the taxonomy of the family recognized 76 viral species, 13 of which have humans as their natural hosts^[502]. In this taxonomy, BKV is listed as human polyomavirus 1, abbreviated as BKVvV, JCV is listed as human polyomavirus 2, abbreviated as JCPyV, and Merkel virus is listed as human polyomavirus 8, abbreviated as MCPyV. No doubt this virus family will have a center

stage in organ transplantation and probably in other immunocompromised states in the years to come.

Key points of part C

Reduction of immunosuppression is the first step in the treatment of symptomatic BKV infection; certain classes of anti-rejection medications are less prone to facilitate BKV replication; the clinical usefulness of drugs putatively inhibiting BKV replication is disputed. The toxicities of these drugs are important; the lists of papovaviruses and of human diseases attributed to them are expanding. Papovavirus-related diseases will be a major study topic in the future.

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