Published in final edited form as:
Bone Marrow Transplant. 2008 January ; 41(1): 11–18. doi:10.1038/sj.bmt.1705886.

Polyomavirus BK infection in blood and marrow transplant recipients

LK Dropulic[1] and **RJ Jones**[2]

[1]Department of Medicine, Johns Hopkins Medical Institutions, Baltimore, MD, USA

[2]Department of Oncology, Johns Hopkins Medical Institutions, Baltimore, MD, USA

Abstract

The association of BK virus infection with hemorrhagic cystitis in blood and marrow transplant (BMT) recipients was first demonstrated two decades ago. During this time, therapeutic interventions focused on supportive measures such as hyperhydration, continuous bladder irrigation and topical administration of agents that alter the mucosal surface of the bladder wall. In recent years, PCR amplification of viral DNA in the urine and plasma has solidified the association of BK virus infection with hemorrhagic cystitis, demonstrating that higher urine and plasma viral loads occur in the setting of disease. The evaluation of virus-specific therapy has lagged behind assessment of the viral load and theories of pathogenesis. Extrapolating from successes in the treatment of BK virus nephropathy in the renal transplant population, cidofovir and leflunomide are identified as potential effective agents for the treatment of BK virus-associated hemorrhagic cystitis. The fluoroquinolone antibiotics may prove to be effective as prophylactic agents. Given the manifestation of BK virus infection in organs outside of the urinary tract in an increasing immunocompromised patient population and the availability of potential antiviral agents, therapeutic trials need to progress beyond the small case series in order to improve the morbidity and mortality caused by BK virus-associated hemorrhagic cystitis in the BMT population.

Keywords

polyomavirus BK; infection; hemorrhagic cystitis; virus-specific therapy

Introduction

Polyomavirus BK was first reported to be a human pathogen in 1971 when a renal transplant patient, with the initials BK, presented with ureteric stenosis.[1] Microbiologic and pathologic work-up identified the BK virus in ureteral epithelial cells. Subsequent reports of BK involvement in clinical disease were few until the 1980s, during the advent of more potent immunosuppressive medications, such as cyclosporine and antithymocyte globulin. In the mid-1980s, the association of BK virus infection with hemorrhagic cystitis was demonstrated in the bone marrow transplant population.[2–4] In the 1990s, in the era of mycophenolate mofetil use, the BK virus became an emerging pathogen in the field of renal transplantation because of its ability to cause infection of the allograft (BK virus nephropathy) and result in allograft loss.[5,6] In this review, we focus on hemorrhagic cystitis,

Correspondence: Dr LK Dropulic, Department of Medicine, The Johns Hopkins University School of Medicine, 1830 East Monument Street, Room448, Baltimore, MD 21205, USA. lesia@jhmi.edu.

the primary manifestation of BK virus infection in the blood and marrow transplant (BMT) recipient. We discuss the clinical manifestations, risk factors, current theories on the pathogenesis and management of hemorrhagic cystitis in the BMT population. In addition, we discuss other potential manifestations of BK virus infection in this patient population that are emerging as the general immunocompromised population grows in the setting of new immunosuppressive agents.

Virology and epidemiology

Polyomavirus hominis 1, the BK virus, is a non-enveloped, encapsulated DNA virus that belongs to the Papovaviridae family. The JC virus and simian virus 40 (SV40) are also members of this family whose genomes share approximately 70% homology with the BK virus.[7] JC virus is a neurotropic virus that is strongly associated with progressive multifocal leukoencephalopathy that occurs in patients with human immunodeficiency virus infection, with hematologic malignancies or in those who are receiving immunosuppressive therapy to prevent allograft rejection or to treat chronic inflammatory or autoimmune diseases.[8] More recently, progressive multifocal leukoencephalopathy has been diagnosed in patients treated with monoclonal antibodies against α4 integrins[9] and in patients receiving rituximab for systemic lupus erythematosis.[10] SV40 infects Asian macaques; however, reports of human infection have appeared.[11,12]

BK virus infection occurs during the early-childhood years and is asymptomatic or associated with fever and mild upper respiratory symptoms.[13] Up to 90% of adults are seropositive.[7] Transmission is believed to occur via the respiratory route but this has not been formally proven. After primary infection, BK virus enters a latent state and resides in uroepithelial cells and possibly lymphocytes.[14] Whether lymphocytes are a site of true latency versus targets of recent or reactivated infection has not been conclusively determined. Other reservoirs of latent infection are possible but are currently not known. The virus remains quiescent unless a natural or iatrogenic state of immunosuppression is imposed. For example, shedding of BK virus in the urine (BK viruria) has been detected in pregnant women and in the elderly.[15,16] The shedding of virus is also frequently detected in the HIV/AIDS population.[17] The greatest incidence of shedding occurs in patients who are therapeutically immunosuppressed in the setting of organ or BMT.[2–4,18]

BK virus infection and genitourinary tract disease

Overall, BK viruria occurs in about 50% of patients after BMT, usually within 2 months of transplantation.[2,3,7] The incidence of BK viruria is similar in allogeneic (range 46–53%) and autologous (range 39–54%) marrow recipients.[19,20] Because of BK virus tropism for the genitourinary epithelium, genitourinary tract disease is the most common manifestation of BK infection in transplant recipients. BK viruria has been associated with a variety of clinical manifestations in BMT recipients, including asymptomatic hematuria, hemorrhagic cystitis, ureteral stenosis and interstitial nephritis.[7,14] Hemorrhagic cystitis is the most prevalent of these complications, occurs in 10–25% of BMT recipients and is associated with significant morbidity and mortality.[2,7,19]

Both non-infectious and infectious hemorrhagic cystitis occurs in BMT recipients (Table 1). Non-infectious cystitis results from the direct cytotoxic effects of antineoplastic treatment, most commonly the alkylating agents cyclophosphamide and ifosfamide.[21] Toxicity to the bladder epithelium following treatment with cyclophosphamide or ifosfamide is caused by a renally excreted metabolite of these agents, acrolein.[22] Acrolein-induced hemorrhagic cystitis occurs in the early post transplant setting, usually within 72 h of receiving the preparative regimen. BK virus-induced hemorrhagic cystitis occurs later after transplant, usually in the post-engraftment period. Now with effective uroprophylaxis (forced diuresis

or MESNA) of acrolein toxicity, virtually all hemorrhagic cystitis after BMT is related to BK virus.[19]

Patients with hemorrhagic cystitis experience urgency, frequency of urination and dysuria due to inflammation of the bladder mucosa. Suprapubic pain and bladder spasms may be present. Patients experience variable degrees of hematuria, hence a grading system was developed to assess the severity of hemorrhagic cystitis. Droller *et al.*[23] proposed the following grades: grade 1, microscopic hematuria; grade 2, macroscopic hematuria; grade 3, macroscopic hematuria with small clots; and grade 4, gross hematuria with clots causing urinary tract obstruction requiring instrumentation for clot removal. Although rarely life-threatening, hemorrhagic cystitis can be a major cause of morbidity including severe pain, uncontrollable bleeding, acute renal failure and prolonged hospitalization.

Association of BK virus infection with hemorrhagic cystitis

Initial studies identified a qualitative association between BK virus and late hemorrhagic cystitis.[2,4,19] Hemorrhagic cystitis was noted to occur four times more frequently in patients who excreted BK virus than in those who did not.[2] In addition, BK viruria was noted to precede or coincide with the onset of disease.[2] However, about 40–50% of BMT patients with persistent viruria remained free of hemorrhagic cystitis, indicating that other factors contributed to the development of hemorrhagic cystitis.[19,24] To strengthen the association of BK virus with hemorrhagic cystitis, subsequent studies demonstrated a quantitative association between hemorrhagic cystitis and BK viruria, revealing that patients with hemorrhagic cystitis tend to have higher peak urine viral loads and excrete much larger amounts of BK virus in the urine.[20,24–26] BK viremia has been shown to be a sensitive and specific indicator of BK virus nephropathy in renal transplant recipients.[27] Similarly, a recent study by Erard *et al.*[28] revealed in a multivariate model that BK viremia was strongly associated with the risk of developing hemorrhagic cystitis. Patients with a plasma viral load greater than 10^4 copies/ml had a significantly higher risk of having hemorrhagic cystitis than patients with a viral load less than 10^4 copies/ml. However, this observation has not been made in other studies[24,25] The association between BK and hemorrhagic cystitis has been further refined by seroepidemiologic studies that revealed that patients who develop a higher peak urine viral load, and hence are at increased risk of developing hemorrhagic cystitis, were more likely to have higher anti-BK virus antibody titers pre-BMT.[25]

The pathogenesis of BK virus-associated hemorrhagic cystitis

Given that many patients have BK viruria and all do not develop hemorrhagic cystitis, what factors are required for post-engraftment hemorrhagic cystitis to occur? BK virus-associated hemorrhagic cystitis likely arises from complementing determinants in the host, the target organ and in the virus in the setting of immunosuppression.[7] Evidence of prior infection in the host, presence of anti-BKV IgG prior to transplant, has been associated with BK viruria, which occurs secondary to reactivation of virus from a latent state.[3,25] Acute GVHD, the particular conditioning regimen, specific BK subtypes and the magnitude of the BK urine viral load have been identified as additional risk factors for BK virus-associated hemorrhagic cystitis[25,26,29] (Table 2). The alloimmune reaction, characteristic of GVHD, or its treatment is suspected to play a significant role in the pathogenesis of BK virus-associated hemorrhagic cystitis, as severe post-engraftment hemorrhagic cystitis is rare in recipients of autologous transplant recipients who receive a similar myeloablative conditioning regimen as their allogeneic counterparts.[29] Hence, most cases of post-engraftment hemorrhagic cystitis occur in allogeneic hematopoietic stem cell transplants with GVHD.[29–31] Bedi *et al.*[19] and Binet *et al.*[32] suggested an immune reconstitution pattern of disease, whereby the disease manifestations are most severe when the immune

systemis reconstituting and viral antigens in the bladder wall are recognized by emerging, functioning lymphocytes.[33] Immune reconstitution disease has been described with JC virus (JCV) and progressive multifocal leukoencephalopathy in AIDS patients receiving highly active antiretroviral therapy (HAART).[34,35]

Three phases of pathogenesis have been proposed by Leung *et al.*[36] (Table 3). First, chemotherapeutic agents and/or radiation used in the conditioning regimen damage the uroepithelium and provide a suitable environment for BK virus replication. Unchecked BK virus replication, in the absence of functional immunity, leads to cytopathic effects. In the post-engraftment period, return or development of anti-BK virus immunity causes extensive mucosal damage and hemorrhage. This proposed model of pathogenesis for BK virus-associated hemorrhagic cystitis has yet to be proven in an animal model. Moreover, some have questioned the role of the immune system in disease pathogenesis, as late, post-engraftment hemorrhagic cystitis has occurred in patients with very low lymphocyte counts (< 100 cells/μl) and in patients receiving high-dose steroids.[28]

The diagnosis of BK virus-associated hemorrhagic cystitis

The diagnosis of hemorrhagic cystitis is considered when hematuria is detected on urinalysis or grossly in the early post-transplant or post-engraftment period. Other clinical features include dysuria, frequency, urgency, suprapubic pain and possible complications of urinary tract obstruction and/or renal failure if bleeding and clot formation is severe. As discussed, early onset hemorrhagic cystitis is usually attributed to the toxic effects of chemoirradiation (Table 1). Late-onset hemorrhagic cystitis, occurring post-engraftment, is linked to BK virus reactivation and presence of the virus is sought. Viral culture is not used for detection of BK virus replication because growth of the virus in tissue culture can take weeks. Cytologic examination of urine can detect characteristic polyomavirus-infected cells, decoy cells, with enlarged nuclei containing a single large basophilic intranuclear inclusion[37] (Figure 1). The limitations of cytology include that these decoy cells can be confused with malignant cells and that infection caused by JC virus or adenovirus can result in similar cytopathology. Therefore, the modality of choice for detecting BK virus in the urine is the PCR for detection of viral DNA. However, detection of BK virus DNA by PCR does not have high disease specificity because BMT patients without hemorrhagic cystitis can excrete BK virus.[2,19,24] Other features of reactivated viral replication can be utilized to link BK virus replication to the cause of hemorrhagic cystitis: detection of viruria prior to the onset of hematuria, high, peaking urine viral loads (10^9–10^{10} copies/ml or greater or ≥ 3 log increase from baseline) and the presence of plasma viremia > 10^4 copies/ml.[2,25,28] Biopsy of bladder epithelium has occasionally been performed and BK DNA has been detected by *in situ* hybridization in the uroepithelium.[28] Patients with post-engraftment hemorrhagic cystitis should have a BK virus DNA load in urine determined at the onset of cystitis and weekly thereafter. If significant hematuria continues for 2 weeks, accompanied by a significant increase in viral load, treatment with cidofovir can be considered. If BK virus is not detected in the urine via cytology or the PCR, PCR amplification for adenovirus or CMV DNA sequences should be performed as these viruses have been reported to play an etiologic role, albeit at much lower frequency, in hemorrhagic cystitis.[38–40]

Treatment of hemorrhagic cystitis

The therapeutic approach to hemorrhagic cystitis will vary and depends on the severity and dynamics of the given episode. In general, treatment is supportive and accompanied by interventions that are designed to control bleeding. The current standard of care for hemorrhagic cystitis related to chemotherapy or BK virus infection is symptomatic and includes analgesia, hyperhydration, forced diuresis and continuous bladder irrigation to

prevent clot formation and renal obstruction. Maintenance of platelets above 50 000 and a hematocrit of 25 in patients with ≥ grade 2 hematuria can alleviate the severity and consequences of hematuria. Mild cases of BK virus-associated hemorrhagic cystitis usually resolve spontaneously over a 2-week period with supportive care. With significant bleeding, severe urinary tract obstruction may occur because of clot formation. In this situation, cystoscopy for clot evacuation and possible cauterization must be performed to preserve renal function. When conservative measures fail and/or when bleeding is intractable and life-threatening, surgical intervention, cystectomy, must be considered.[41] Instillation of topical agents, such as alum, formalin and prostaglandin E1, into the bladder is used by some clinicians; however, the efficacy of these approaches remains controversial due to the absence of controlled studies and the possibility of long-term morbidity.[42]

To date, no antiviral drug with proven efficacy against BK virus replication has been licensed. However, due to the strong clinical demand for treatments for BK virus-associated nephropathy in renal transplant recipients and for hemorrhagic cystitis in BMT patients, several drugs that have not been studied in depth *in vitro* have been tested in small clinical series (Table 4). One such drug is cidofovir, which is an acyclic nucleoside analog with antipolyomavirus activity that has been demonstrated in *in vitro* studies to have activity against BK virus.[43] Cidofovir is licensed for the treatment of CMV retinitis in AIDS patients and is a second-line drug for the treatment of ganciclovir-resistant CMV infections.[44,45] Cidofovir inhibits CMV replication by inhibiting the viral DNA polymerase. The mechanism by which cidofovir inhibits BK virus replication is not clear. The BK virus genome does not encode a DNA polymerase. Investigators speculate that cidofovir may inhibit a functional domain of the BKV large T antigen that possesses DNA polymerase activity.[46,47] Or, given that this drug is a nucleoside analog, the antiviral effect may be the result of inhibition of viral DNA synthesis.[47] Recent systematic *in vitro* studies of the effect of cidofovir on BK virus replication using real-time PCR revealed only a modest effect of cidofovir on BK virus replication.[48]

Cidofovir has been used to treat BK virus nephropathy in renal transplant recipients with some success; however, the studies were not randomized and controlled.[49,50] Cidofovir has been used to treat hemorrhagic cystitis is BMT patients.[51,52] Held *et al.* treated hemorrhagic cystitis in an allogeneic hematopoietic stem cell transplant recipient with BKV-associated hemorrhagic cystitis and concomitant CMV reactivation. Cidofovir treatment resulted in a sustained suppression of CMV replication and a significant reduction of BK viruria accompanied by clinical improvement. Savona *et al.*[52] treated 19 hematopoietic stem cell transplant recipients with weekly low-dose cidofovir.[52] A clinical response was detected in 84% of patients; however, a virologic response, a decreased viral load in the urine, was detected in only 47%. All patients with a virologic response had a clinical response. Other investigators have reported successful treatment of hemorrhagic cystitis with systemic or intravesicular cidofovir, noting elimination or a decrease in the urine viral load.[42,53]

Leflunomide belongs to the class of drugs called malononitrilamides and is an immunosuppressive agent that is licensed for the treatment of rheumatoid arthritis.[54] Leflunomide exhibits its immunosuppressive activity by inhibiting protein kinase activity and pyrimidine synthesis.[55] In addition, leflunomide has antiviral activity *in vitro* against CMV, herpes simplex virus and BK virus.[48,56] Leflunomide has been used to treat renal transplant patients with biopsy-proven BK nephropathy.[57,58] Patients who maintained a minimal blood concentration of active drug either cleared or had a significant reduction in BK viral load in blood and urine and experienced stabilized or improved serum creatinine levels. The incidence of graft loss was low, 15% (usually 35–65%), likely due to the immunosuppressive activity of leflunomide.[58] Leflunomide has been used in allogeneic BMT recipients for the treatment of resistant/refractory cytomegalovirus infections with

variable success.[59,60] Reports of treatment of BK associated-hemorrhagic cystitis with leflunomide have not appeared in the literature to date. However, given this agent's antiviral activity against BK virus, leflunomide should be considered as a potential agent to treat BK-virus associated hemorrhagic cystitis.

Almost two decades ago, studies demonstrated that fluoroquinolone antibiotics, nalidixic acid and oxolinic acid, can inhibit BK virus replication *in vitro*.[61,62] Quinolone antibiotics inhibit bacterial replication by inhibiting the activity of type II topoisomerases, including gyrase and topoisomerase IV. Investigators speculate that these DNA gyrase inhibitors may inhibit BK virus replication by inhibiting the helicase activity of the polyomavirus large T antigen that has a function similar to the DNA gyrase. Recently, investigators demonstrated that clinically relevant fluoroquinolones, such as levofloxacin, trovofloxacin, ciprofloxacin, ofloxacin and gatifloxacin, inhibit BK or SV40 viral replication and block the cytopathic effect of SV40 in monkey cells.[63,64] In addition, the investigators demonstrated that fluoroquinolones appear to work by blocking the helicase activity of purified SV40 T antigen.[64]

Two recent clinical studies demonstrated the potential utility of treating BK virus infection in BMT patients with fluoroquinolones. A study in allogeneic hematopoietic stem cell transplant recipients revealed that patients treated with prophylactic ciprofloxacin had a significantly decreased peak urine BK viral load and a decreased incidence of hemorrhagic cystitis compared to patients treated with cephalosporins.[65] A study performed in renal transplant patients with gatifloxacin (pulled from the market in 2006) revealed that 7/10 patients with active BK virus replication in the urine or plasma had a > 80% reduction in viremia or a disappearance of decoys cells in the urine.[66] Randhawa *et al.*[63] have demonstrated that the antiviral activity of the fluoroquinolone antibiotics was modest and exhibited a low selectivity index (ratio of drug concentration that results in 50% reduction of host cell replication to the drug concentration that results in 50% reduction in viral replication). Therefore, fluoroquinolone antibiotics may be more effective as prophylactic agents against BK virus-associated hemorrhagic cystitis rather than therapeutic agents.

Controlled clinical trials of cidofovir, leflunomide and fluoroquinolones for the treatment of BK virus-associated hemorrhagic cystitis are needed to determine their true safety and efficacy in this patient population. However, if hematuria is recalcitrant, not responding to supportive measures, and instillation of topical agents is deemed to be associated with potential serious complications, consider administration of intravenous cidofovir, especially to those patients with a significant increase in urinary BK viral load (≥ 3 log)[24,20,25,26] or with plasma viremia (viral load > 10^4 copies/ml).[28]

Non-genitourinary tract manifestations of BK virus infection in blood and marrow recipients

BK virus associated tubulointerstitial nephritis or nephropathy is an infection primarily encountered in the allograft of renal transplant patients.[27] However, in recent years, several cases of BK nephritis in the native kidneys of BMT recipients, not always accompanied by hemorrhagic cystitis, have been reported.[67–70] A report of bilateral ureteral obstruction possibly related to ureteritis caused by BK virus infection in a BMT recipient has also been reported.[71]

In recent years, clinical manifestations of BK virus infection in organ systems outside of the genitourinary tract have been reported[14] (Table 5). Some investigators speculate that this may be secondary to the effects of more potent immunosuppressive agents combined with a larger immunosuppressed patient population. Whereas JC virus is the polyomavirus usually

associated with central nervous system infection, in recent years, meningitis and meningoencephalitis caused by BK virus have been reported in patients with hematologic malignancies or AIDS.[72–77] A case of bilateral atypical retinitis occurred in a patient with AIDS.[78] Interestingly, investigators have identified rearranged regulatory regions of BK virus isolated from the central nervous system, implying that these genetic changes may play a role in neurovirulence.[72,75] Similar rearranged regulatory regions have been described for JC virus causing progressive multifocal leukoencephalopathy.[79]

BK virus infection of the lungs has been reported. A fatal case of BK viral pneumonia occurred in an infant who received an unrelated umbilical cord transplant.[80] The pneumonia followed the diagnosis of hemorrhagic cystitis. Fatal pneumonia caused by BK virus was diagnosed in a patient with CLL.[81] The diagnosis in these cases was made by cell culture and/or immunohistochemistry and PCR using lung tissue. In both cases, an extensive pattern of diffuse alveolar damage was a prominent histologic finding. A case of disseminated infection associated with pneumonia, nephritis and meningoencephalitis in a patient with the AIDS and a case of fatal vasculopathy caused by a necrotizing endothelial infection in a renal transplant recipient have been reported.[74,82] Our group has detected BK virus at autopsy in the lungs, liver and gut of BMT patients dying of undefined multi-organ failure (unpublished).

Future directions

BK virus has emerged as an important pathogen in the solid organ transplant and BMT populations. As these populations grow and new immunosuppressive therapies are developed, the incidence and diversity of presentations of this virus, once thought to be confined to the uroepithelium, are expected to increase. Hence, randomized-controlled multicenter studies that determine the true efficacy of the currently available candidate anti-BK virus therapies are needed. The fluoroquinolone antibiotics should be evaluated as a prophylactic therapy and cidofovir and leflunomide as therapeutic agents. Development of new agents with antiviral activity targeted to specific steps in the BK virus replication cycle should be encouraged.

References

1. Gardner SD, Field AM, Coleman DV, Hulme B. New papovavirus (B.K.) isolated from urine after renal transplantation. Lancet. 1971; 1:253–257.
2. Arthur RR, Shah KV, Baust SJ, Santos GW, Saral R. Association of BK viruria with hemorrhagic cystitis in recipients of bone marrow transplants. N Engl J Med. 1986; 315:230–234. [PubMed: 3014334]
3. Arthur RR, Shah KV, Charache P, Saral R. BK and JC virus infections in recipients of bone marrow transplants. J Infect Dis. 1988; 158:563–569. [PubMed: 2842404]
4. Apperley JF, Rice SJ, Bishop JA, Chia YC, Krausz T, Gardner SD, et al. Late-onset hemorrhagic cystitis associated with urinary excretion of polyomaviruses after bone marrow transplantation. Transplantation. 1987; 43:108. [PubMed: 3026070]
5. Pappo O, Demetris AJ, Raikow RB, Randhawa PS. Human polyoma virus infection of renal allografts: histopathologic diagnosis, clinical significance, and literature review. Mod Pathol. 1996; 9:105–109. [PubMed: 8657714]
6. Randhawa PS, Demetris AJ. Nephropathy due to polyomavirus type BK. N Engl J Med. 2000; 342:1361–1363. [PubMed: 10793170]
7. Hirsch HH, Steiger J. Polyomavirus BK. Lancet Infect Dis. 2003; 3:611–623. [PubMed: 14522260]
8. Khalili K, Gordon J, White MK. The polyomavirus, JCV and its involvement in human disease. Adv Exp Med Biol. 2006; 577:274–287. [PubMed: 16626043]

9. Yousry TA, Major EO, Ryschkewitsch C, Fahle G, Fischer S, Hou J, et al. Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy. N Engl J Med. 2006; 354:924–933. [PubMed: 16510746]
10. Steurer M, Clausen J, Gotwald T, Gunsilius E, Stockhammer G, Gastl G, et al. Progressive multifocal encephalopathy after allogeneic stem cell transplantation and posttransplantation rituximab. Transplantation. 2003; 76:435–436. [PubMed: 12883208]
11. Milstone A, Vilchez RA, Geiger X, Fogo AB, Butel JS, Dummer S. Polyomavirus simian virus 40 infection associated with nephropathy in lung-transplant recipient. Transplantation. 2004; 77:1019–1024. [PubMed: 15087764]
12. Li RM, Branton MH, Tanawattanacharoen S, Falk RA, Jennette JC, Kopp JB. Molecular identification of SV40 infection in human subjects and possible association with kidney disease. J Am Soc Nephrol. 2002; 13:2320–2330. [PubMed: 12191976]
13. Goudsmit J, Wertheim-van Dillen P, van Strien A, van der NJ. The role of BK virus in acute respiratory tract disease and the presence of BK virus DNA in tonsils. J Med Virol. 1982; 10:91–99. [PubMed: 6292361]
14. Reploeg MD, Storch GA, Clifford DB. BK virus: a clinical review. Clin Infect Dis. 2001; 33:191–202. [PubMed: 11418879]
15. Coleman DV, Gardner SD, Mulholland C, Fridiksdottir V, Porter AA, Lilford R, et al. Human polyomavirus in pregnancy a model for the study of defense mechanisms to virus reactivation. Clin Exp Immunol. 1983; 53:289–296. [PubMed: 6309442]
16. Kitumura T, Aso Y, Kuniyoshi N, Hara K, Yogo Y. High incidence of urinary JC virus excretion in nonimmunosuppressed older patients. J Infect Dis. 1990; 161:1128–1133. [PubMed: 2161040]
17. Behzad-Behbahani A, Klapper PE, Vallely PJ, Cleator GM, Khoo SH. Detection of BK virus and JC virus DNA in urine samples in immunocompromised (HIV-infected) and immunocompetent (HIV-non-infected) patients using polymerase chain reaction and microplate hybridization. J Clin Virol. 2004; 29:224–229. [PubMed: 15018849]
18. Munoz P, Fogeda M, Bouza E, Verde E, Palomo J, Banares R. Prevalence of BK virus replication among recipients of solid organ transplants. Clin Infect Dis. 2005; 41:1720–1725. [PubMed: 16288394]
19. Bedi A, Miller CB, Hanson JL, Goodman S, Ambinder RF, Charache P, et al. Association of BK virus with failure of prophylaxis against hemorrhagic cystitis following bone marrow transplantation. J Clin Oncol. 1995; 13:1103–1109. [PubMed: 7738616]
20. Azzi A, Cesaro S, Laszlo D, Zakrzewska K, Ciappi S, De Santis R, et al. Human polyomavirus BK (BKV) load and hemorrhagic cystitis in bone marrow transplant patients. J Clin Virol. 1999; 14:79–86. [PubMed: 10588450]
21. Anderson EE, Cobb OE, Glenn JF. Cyclophosphamide hemorrhagic cystitis. J Urol. 1967; 97:857–858. [PubMed: 6025931]
22. Cox PJ. Cyclophosphamide cystitis—identification of acrolein as the causative agent. Biochem Pharmacol. 1979; 28:2045–2049. [PubMed: 475846]
23. Droller MJ, Saral R, Santos G. Prevention of cyclophosphamide-induced hemorrhagic cystitis. Urology. 1982; 20:256–258. [PubMed: 7123717]
24. Leung AYH, Seun CKM, Lie AKW, Liang RHS, Yuen KY, Kwong YL. Quantification of polyoma BK viruria in hemorrhagic cystitis complicating bone marrow transplantation. Blood. 2001; 98:1971–1978. [PubMed: 11535537]
25. Wong SY, Chan K-H, Cheng VCC, Yuen K-Y, Kwong Y-L, Leung AYH. Relationship of pretransplantation polyoma BK virus serologic findings and BK viral reactivation after hematopoietic stem cell transplantation. Clin Infect Dis. 2007; 44:830–837. [PubMed: 17304456]
26. Bogdanovic G, Priftakis P, Giraud G, Kuzniar M, Ferraldeschi R, Kokhaei P, et al. Association between a high BK virus load in urine samples of patients with graft-versus-host disease and development of hemorrhagic cystitis after hematopoietic stem cell transplantation. J Clin Microbiol. 2004; 42:5394–5396. [PubMed: 15528753]
27. Nickeleit V, Klimkait T, Binet IF, Dalquen P, Del Zenero V, Thiel G, et al. Testing for polyomavirus type BK DNA in plasma to identify renal allograft recipients with viral nephropathy. N Engl J Med. 2000; 342:1309–1315. [PubMed: 10793163]

28. Erard V, Kim HW, Corey L, Limaye A, Huang M-L, Myerson D, et al. BK DNA viral load in plasma: evidence for an association with hemorrhagic cystitis in allogeneic hematopoietic cell transplant recipients. Blood. 2005; 106:1130–1132. [PubMed: 15845896]
29. Leung AYH, Mak R, Lie AKW, Yuen KY, Cheng VCC, Liang R, et al. Clinicopathological features and risk factors of clinically overt hemorrhagic cystitis complicating bone marrow transplantation. Bone Marrow Transplant. 2002; 29:509–513. [PubMed: 11960271]
30. Leung AYH, Chan M, Cheng VCC, Lie AKW, Yuen K-Y, Kwong Y-L. Polyoma BK viruria in patients undergoing autologous hematopoietic stem cell transplantation. Bone Marrow Transplant. 2005; 35:1029–1030. [PubMed: 15806127]
31. Seber A, Shu XO, Defor T, Sencer T, Ramsay N. Risk factors for severe hemorrhagic cystitis following BMT. Bone Marrow Transplant. 1999; 23:35–40. [PubMed: 10037048]
32. Binet I, Nickeleit V, Hirsch HH. Polyomavirus infections in transplant recipients. Curr Opin Organ Transplant. 2000; 5:210–216.
33. Cheng VCC, Yuen K-Y, Chan W-M, Wong SSY, Edmond SKM, Chan RMT. Immune reconstitution disease involving the innate and adaptive responses. Clin Infect Dis. 2000; 30:882–892. [PubMed: 10880300]
34. Safdar A, Rubocki RJ, Horvath JA, Narayan KK, Waldron RL. Fatal immune restoration disease in human immunodeficiency virus type-1 infected patients with progressive multifocal leukoencephalopathy: impact of antiretroviral therapy-associated immune reconstitution. Clin Infect Dis. 2002; 35:1250–1257. [PubMed: 12410486]
35. D'Amico R, Sarkar S, Yusuff J, Azar E, Perlman DC. Immune reconstitution after potent antiretroviral therapy in AIDS patients with progressive mutifocal leukoencephalopathy. Scand J Infect Dis. 2007; 39:347–350. [PubMed: 17454900]
36. Leung AYH, Yuen K-Y, Kwong Y-L. Polyoma BK virus and haemorrhagic cystitis in haematopoietic stem cell transplantation: a changing paradigm. Bone Marrow Transplant. 2005; 36:929–937. [PubMed: 16184185]
37. Fogazzi GB, Cantu M, Saglimbeni L. Decoy cells in the urine due to polyomavirus BK infection: easily seen by phase contrast microscopy. Nephrol Dial Transplant. 2001; 16:1496–1498. [PubMed: 11427650]
38. Ambinder RF, Burns W, Forman M, Charache P, Arthur R, Beschorner W, et al. Hemorrhagic cystitis associated with adenovirus infection in bone marrow transplantation. Arch Int Med. 1986; 146:1400–1401. [PubMed: 3013110]
39. Akiyama H, Kurosu T, Sakashita C, Inoue T. Adenovirus is a key pathogen in hemorrhagic cystitis associated with bone marrow transplantation. Clin Infect Dis. 2001; 32:1325. [PubMed: 11303268]
40. Spach DH, Bauwens JE, Myerson D, Mustafa MM, Bowden RA. Cytomegalovirus-induced hemorrhagic cystitis following bone marrow transplantation. Clin Infect Dis. 1993; 16:142–144. [PubMed: 8383546]
41. Sebe P, Garderet L, Traxer O, Nouri M, Gluckman E, Gattegno B. Subtotal cytectomy with ileocystoplasty for severe hemorrhagic cystitis after bone marrow transplantation. Urology. 2001; 57l:168xiv–168xvi. [PubMed: 11164170]
42. Gorczynska E, Turkiewicz D, Rybka K, Toporski J, Kalwak K, Dyla A, et al. Incidence, clinical outcome, and management of virus-induced hemorrhagic cystitis in children and adolescents after allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2005; 11:797–804. [PubMed: 16182180]
43. De Clercq E, Holy A. Acyclic nucleoside phosphonates: a key class of antiviral drugs. Nat Rev Drug Discov. 2005; 4:928–940. [PubMed: 16264436]
44. Dunn JP, Van Natta M, Foster G, Kuppermann BD, Martin DF, Zong A, et al. Complications of ganciclovir implant surgery in patients with cytomegalovirus retinitis: the ganciclovir cidifovir cytomegalovirus retinitis trial. Retina. 2004; 24:41–50. [PubMed: 15076943]
45. Preiksaitis JK, Brennan DC, Fishman J, Allen U. Canadian society of transplantation consensus workshop of cytomegalovirus management in solid organ transplantation final report. Am J Transplant. 2005; 5:218–227. [PubMed: 15643981]

46. Randhawa P, Farasati NA, Shapiro R, Hostetler KY. Ether lipid ester derivatives of cidofovir inhibit polyomavirus BK replication *in vitro*. Antimicrob Agents Chemother. 2006; 50:1564–1566. [PubMed: 16569886]
47. Josephson MA, Williams JW, Chandraker A, Randhawa PS. Polyomavirus-associated nephropathy: update on antiviral strategies. Transpl Infect Dis. 2006; 8:95–101. [PubMed: 16734632]
48. Farasati NA, Shapiro R, Vats A, Randhawa P. Effect of leflunomide and cidofovir on replication of BK virus in an *in vitro* culture system. Transplantation. 2005; 79:116–118. [PubMed: 15714178]
49. Vats A, Shapiro R, Randhawa SP, Scantlebury V, Tuzuner A, Saxena M, et al. Quantitative viral load monitoring and cidofovir therapy for management of BK virus-associated nephropathy in children and adults. Transplantation. 2003; 75:105–112. [PubMed: 12544881]
50. Kadambi PV, Josephson MA, Williams J, Corey L, Jerome KR, Meehan SM, et al. Treatment of refractory BK virus-associated nephropathy with cidofovir. Am J Transplant. 2003; 3:186–191. [PubMed: 12614296]
51. Held TK, Biel SS, Nitsche A, Kurth A, Chen S, Gelderblom HR, et al. Treatment of BK virus-associated hemorrhagic cystitis and simultaneous CMV reactivation with cidofovir. Bone Marrow Transplant. 2000; 26:347–350. [PubMed: 10967578]
52. Savona MR, Newton D, Frame D, Levine JE, Mineishi S, Kaul DR. Low-dose cidofovir treatment of BK virus-associated hemorrhagic cystitis in recipients of hematopoietic stemcell transplant. Bone Marrow Transplant. 2007; 39:783–787. [PubMed: 17438584]
53. Bridges B, Donegan S, Badros A. Cidofovir bladder instillation for the treatment of BK hemorrhagic cystitis after allogeneic stemcell transplantation. Am J Hematol. 2006; 81:531–537.
54. Strand V, Cohen S, Schiff M, Weaver A, Fleischmann R, Cannon G, et al. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. Arch Intern Med. 1999; 159:2542–2550. [PubMed: 10573044]
55. Rinaldo CH, Hirsch HH. Antivirals for the treatment of polyomavirus BK replication. Expert Rev Anti Infect Ther. 2007; 5:105–115. [PubMed: 17266458]
56. Waldman WJ, Knight DA, Blinder L, Shen J, Lurain NS, Miller DM, et al. Inhibition of cytomegalovirus *in vitro* and *in vivo* by the experimental immunosuppressive agent leflunomide. Intervirology. 1999; 42:412–418. [PubMed: 10702725]
57. Williams JW, Javaid B, Kadambi PV, Gillen D, Harland R, Thistlewaite JR, et al. Leflunomide for polyomavirus type BK nephropathy. N Engl J Med. 2005; 352:1157–1158. [PubMed: 15784677]
58. Josephson MA, Gillen MA, Javaid B, Kadambi P, Meehan S, Foster P, et al. Treatment of renal allograft polyoma BK virus infection with leflunomide. Transplantation. 2006; 81:704–710. [PubMed: 16534472]
59. Avery RK, Bolwell BJ, Yen-Lieberman B, Lurain N, Waldman WJ, Longworth DL, et al. Use of leflunomide in an allogeneic bone marrow transplant recipient with refractory cytomegalovirus infection. Bone Marrow Transplant. 2004; 34:1071–1075. [PubMed: 15489872]
60. Battiwalla M, Paplham P, Almyroudis NG, McCarthy A, Abdelhalim A, Elefante A, et al. Leflunomide failure to control recurrent cyt0omegalovirus infection in the setting of renal failure after allogeneic stemcell transplantation. Transpl Infect Dis. 2007; 9:28–32. [PubMed: 17313468]
61. Ferrazzi E, Peracchi M, Biasolo MA, Faggionato O, Stefanelli S, Palu G, et al. Antiviral activity of gyrase inhibitors norfloxacin, coumermycin A1, and nalidixic acid. Biochem. Pharmacol. 1988; 37:1885–1886. [PubMed: 2837249]
62. Portolani M, Pietrosemoli P, Cermelli C, Mannini-Palenzona A, Grossi MP, Paolini L, et al. Suppression of BK virus replication and cytopathic effect by inhibitors of prokaryotic DNA gyrase. Antiviral Res. 1988; 9:205–218. [PubMed: 2840850]
63. Randhawa PS. Anti-BK virus activity of ciprofloxacin and related antibiotics. Clin Infect Dis. 2005; 41:1366–1367. [PubMed: 16206122]
64. Ali S, Chandraker A, DeCaprio J. Inhibition of polyoma helicase activity by quinolones. J Am Soc Neprhol. 2003; 14:43A.
65. Leung AY, Chan MT, Yuen KY, Cheng VC, Chan KH, Wong CL, et al. Ciprofloxacin decreased polyoma BK virus load in patients who underwent allogeneic hematopoietic stem cell transplantation. Clin Infect Dis. 2005; 40:528–537. [PubMed: 15712075]

66. Chandraker A, Ali S, Drachenberg CB, Ravinder W, Hirsch H, DeCaprio J, et al. Use of fluoroquinolones to treat BK infection in renal transplant recipients. Am J Transplant. 2004; 4(Suppl 8):587.

67. Limaye AP, Smith KD, Cook L, Groom DA, Hunt NC, Jerome KR, et al. Polyomavirus nephropathy in native kidneys of non-renal transplant recipients. Am J Transplant. 2005; 5:614–620. [PubMed: 15707418]

68. Shapiro S, Robin M, Esperou H, Rocha V, Garnier T, Gluckman E, et al. Polyomavirus nephropathy in the native kidneys of an unrelated cord blood transplant recipient followed by a disseminated polyomavirus infection. Transplantation. 2006; 82:292–293. [PubMed: 16858298]

69. Avery RK. BK virus and renal dysfunction. Clin Infect Dis. 2005; 41:1726–1727. [PubMed: 16288395]

70. Stracke S, Helmchen U, von Muller L, Bunjes D, Keller F. Polyoma virus-associated interstitial nephritis in a patient with acute myeloid leukaemia and peripheral blood stem cell transplantation. Nephrol Dial Transplant. 2003; 18:2431–2433. [PubMed: 14551380]

71. Gaston K, Gabriel DA, Lavelle JP. Rare cause of ureteral obstruction. Urology. 2005; 66:1110.e5–1110.e6. [PubMed: 16286146]

72. Stoner GL, Alappan R, Jobes DV, Ryschkewitsch CF, Landry Ml. BK virus regulatory rearrangements in brain and cerebrospinal fluid from a leukemia patient with tubulointerstitial nephritis and meningoencephalitis. Am J Kidney Dis. 2002; 39:1102–1112. [PubMed: 11979356]

73. Vago L, Cinque P, Sala E, Nebuloni M, Calderelli R, Racca S, et al. JCV-DNA and BKV-DNA in the CNS tissue and CSF of AIDS patients and normal subjects. Study of 41 cases and review of the literature. J Acquir Immune Defic Syndr Hum Retrovirol. 1996; 12:139–146. [PubMed: 8680884]

74. Vallbracht A, Lohler J, Gossmann J, Gluck T, Petersen D, Gerth HJ, et al. Disseminated BK type polyomavirus infection in an AIDS patients associated with central nervous system disease. Am J Pathol. 1993; 143:29–39. [PubMed: 8391217]

75. Jorgensen GE, Hammarin AL, Bratt G, Grandien M, Flaegstad T, Johnsen JI. Identification of a unique BK virus variant in the CNS of a patient with AIDS. J Med Virol. 2003; 70:14–19. [PubMed: 12629638]

76. Bratt G, Hammarin AL, Grandien M, Hedquist BG, Nennesmo I, Sundelin B, et al. BK virus as the cause of meningoencephalitis, retinitis and nephritis in a patient with AIDS. AIDS. 1999; 13:1071–1075. [PubMed: 10397537]

77. Lesprit P, Chaline-Lehmann D, Authier FJ, Ponnelle T, Gray F, Levy Y. BK virus encephalitis in a patient with AIDS and lymphoma. AIDS. 2001; 15:1196–1199. [PubMed: 11416733]

78. Hedquist BG, Bratt G, Hammarin AL, Grandien M, Nennesmo I, Sundelin B, et al. Identification of BK virus in a patient with acquired immune deficiency syndrome and bilateral atypical retinitis. Ophthalmology. 1999; 106:129–132. [PubMed: 9917793]

79. Agostini HT, Ryschkewitsch CF, Singer JE, Stoner GL. JC virus regulatory region rearrangments and genotypes in progressive multifocal leukoencephalopathy: two independent aspects of virus variation. J Gen Virol. 1997; 78:659–664. [PubMed: 9049419]

80. Sandler ES, Aquino VM, Goss-Shohet E, Hinrichs S, Krisher K. BK papova virus pneumonia following hematopoietic stem cell transplantation. Bone Marrow Transplant. 1997; 20:163–165. [PubMed: 9244421]

81. Galan A, Rauch CA, Otis CN. Fatal BK polyoma viral pneumonia associated with immunosuppression. Hum Pathol. 2005; 36:1031–1034. [PubMed: 16153469]

82. Petrogiannis-Haliotis T, Sakoulas G, Kirby J, Koralnik IJ, Dvorak AM, Monahan-Earley R, et al. BK-related polyomavirus vasculopathy in a renal transplant recipient. N Engl J Med. 2001; 345:1250–1255. [PubMed: 11680445]

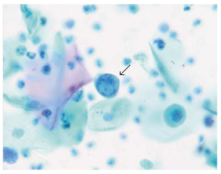

Figure 1.
Cytologic preparation of urine epithelial cells revealing characteristic polyomavirus-infected cells, decoy cells, containing an enlarged nucleus with a single large basophilic intranuclear inclusion (arrows). × 60 magnification (provided by Dr Dorothy Rosenthal).

Table 1

Causes of hemorrhagic cystitis in BMT recipients

Pre-engraftment	Post-engraftment
• Chemotherapeutic agents	• Infections
Cyclophosphamide, ifosfamide	Polyomavirus (BK)
Busulfan	Cytomegalovirus
High-dose etoposide	Adenovirus
• Other	• Other
Pelvic irradiation	Severe thrombocytopenia
Severe thrombocytopenia	Coagulopathy
Coagulopathy	

Abbreviation: BMT=blood and marrow transplant.

Table 2

Potential risk factors for BK virus-associated hemorrhagic cystitis

• Presence of pretransplant BK virus IgG antibody titer
• Type of conditioning regimen (full intensity vs reduced intensity)
• Allogeneic transplant
• Type of donor (unrelated vs related)
• Acute GVHD
• High peak BK urine viral load or greater than 3 log increase in viral load

Table 3

Proposed steps in the pathogenesis of BK virus-associated hemorrhagic cystitis

• Conditioning regimen damages the uroepithelium and provides a milieu for BK virus replication
• Immunosuppressed state promotes reactivation of latent virus
• Unchecked virus replication proceeds in the absence of functional immunity
• Return or development of anti-BK virus immunity causes further mucosal damage and hemorrhage (immune reconstitution)

Table 4

Potential agents for the treatment of BK virus-associated hemorrhagic cystitis

Antiviral agent	Dose	Clinical experience	Proposed mechanisms of action	Major side effects
Fluoroquinolones	Ciprofloxacin 500 mg p.o. twice daily or 200 mg i.v. twice daily	BMT recipients had significantly lower peak urinary viral loads,[65] likely more effective as prophylactic agent	Inhibition of helicase activity of large T antigen; modest anti-BK virus activity *in vitro*[63]	Rash, diarrhea, nausea, dizziness, headache, restlessness; resistance (bacterial and viral)
Cidofovir	Standard dosing regimen: 5 mg/kg i.v. weekly for 2 weeks, then 5 mg/kg with probenecid every other week[42] Low-dose cidofovir: 1 mg/kg i.v. weekly without probenecid[52]	Mostly single case reports with variable results Case series of 19 children, grade ≥2: 80% with clinical response; 32% with resolution of viruria (qualitative PCR)[42] Case series of 19 adults, grades 1–3: clinical response 84%; virologic response 47% (at least 1 log decrease in urinary viral load)[52]	Cytosine analog that inhibits viral DNA synthesis Inhibition of DNA polymerase activity of large T antigen Modest effect on BK virus replication*in vitro*[48]	Rash, nausea, vomiting, headache, nephrotoxicity, neutropenia
Leflunomide	Loading dose of 100 mg/day for 5 days; maintenance dose of 20–60 mg/day with target blood level of 50–100 μg/ml[57]	No hemorrhagic cystitis; treatment of BK nephropathy in renal transplant[57,58] and refractory CMV in BMT[59,60]	Interference with tyrosine kinase phosphorylation of cellular or virally encoded proteins needed for viral replication; modest antiviral effect *in vitro*[48]	Rash, alopecia, diarrhea, hepatotoxicity, pancytopenia, agranulocytosis, thrombocytopenia

Abbreviation: BMT = blood and marrow transplant.

Table 5

Potential clinical manifestations of BK virus infection in BMT recipients

- Genitourinary tract
  - Hemorrhagic cystitis
  - Ureteral stenosis
  - Tubulointerstitial nephritis
- Central nervous system
  - Meningitis
  - Encephalitis
  - Retinitis
- Pneumonitis
- Gastrointestinal infection
- Disseminated infection

Abbreviation: BMT = blood and marrow transplant.