BK Virus in Hematopoietic Stem Cell Transplantation Recipients

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BK virus has become a serious issue in hematopoietic stem cell transplantation recipients, commonly manifesting as hemorrhagic cystitis, which can last from a matter of days to months and, if severe enough, may result in death. Patients with BK virus-associated hemorrhagic cystitis often experience poor quality of life, severe pain and discomfort, and prolonged hospitalizations. Despite numerous advances in stem cell transplantation methods, BK virus-associated hemorrhagic cystitis is difficult to control and treatment options are few. This article provides an overview of BK virus along with risk factors, current treatment modalities, and nursing considerations.

Polyomavirus hominis-type 1, commonly referred to as BK virus, infects up to 90% of the world’s population (Hirsch & Steiger 2003) but does not usually cause symptoms in immunocompetent individuals. However, BK virus can be a very serious issue in immunocompromised patients.

BK virus, which derives its name from the initials of the first infected patient, is troubling to renal and hematopoietic stem cell transplantation recipients. Allograft dysfunction and failure may occur secondary to Polyoma-associated nephropathy in kidney transplantation recipients (Hirsch, 2002). BK virus commonly manifests in hematopoietic stem cell transplantation recipients as hemorrhagic cystitis, characterized by painful hematuria secondary to inflammation and breakdown of epithelial cells of the bladder mucosa (Leung, Yuen, & Kwong, 2005). If severe, hemorrhagic cystitis may be life threatening. BK virus also has been linked to ureteric stenosis, vasculopathy pneumonitis, encephalitis, retinitis, and multi-organ failure (Galan, Rauch, & Otis, 2005; Hirsch & Steiger, 2003). BK virus has proven to be a challenge for patients and healthcare professionals alike. This article provides an overview of BK virus infection in hematopoietic stem cell transplantation recipients, along with risk factors, treatment modalities, and nursing considerations.

**BK Virus: An Overview**

**Virology**

BK is a double-stranded, nonenveloped virus that contains icosahedral capsids. The icosahedral capsids contain the DNA genome (Hirsch & Steiger, 2003). The BK virus genome is very similar to that of Polyomavirus hominis-type 2 (known as JC Virus), which also is found in immunocompromised patients. The BK virus genome is comprised of regulatory, early, and late regions. The regulatory region is referred to as the noncoding region and is the site of replication, containing promoter elements of early and late genes (Hirsch & Steiger). Early genes are responsible for encoding the small tumor antigen and the large tumor antigen. Large tumor antigen plays a pivotal role in BK virus transcription and replication (Hirsch & Steiger). BK virus replication is very dependent on the amenities of host cell enzymes, and the large tumor antigen identifies host cell proteins necessary for replication. Late genes are responsible for encoding viral capsid proteins and the agnoprotein, which serves in viron assembly (Hirsch & Steiger). Late gene expression only occurs after BK virus replication has occurred (see Figure 1).

**BK Virus Disease**

*Infection, replication, and disease* are three terms key to understanding BK virus (see Table 1). BK virus infection is...
determined by evidence of serologic virus exposure, including replicative and latent periods. Latency is a period of nonreplicative infection (Hirsch & Steiger, 2003). Patients usually are asymptomatic during latency periods. BK virus replication is actual evidence of viral multiplication. In this case, BK virus may be detected by cell culture, structural proteins on the mRNA, plasma, colony-stimulating factor analysis, or by cytological or histological evidence (Hirsch & Steiger) (see Figure 2). Patients may not be symptomatic during replicative periods; symptoms depend on the degree of replication and the degree of immunosuppression. BK virus disease will demonstrate organ dysfunction secondary to BK virus replication, and patients almost always present with symptoms (Hirsch & Steiger).

Primary BK virus infection occurs when a seronegative patient converts to seropositive by detection of viral genes or gene products. Secondary infection occurs with BK virus replication in an ongoing seropositive patient (Hirsch & Steiger, 2003). In this case, the patient would demonstrate positive BK virus serology in a period of latency. As replication occurs and the disease is no longer latent, the patient will experience secondary infection. About 5% of healthy individuals will demonstrate low-level replication with asymptomatic viruria (Hirsch & Steiger), but this percentage can increase to more than 60% in patients who are older, pregnant, or have underlying immune dysfunction (Hirsch & Steiger). However, the fact that all people that demonstrate replicative periods do not develop BK virus disease suggests that other factors play a role in development.

**Epidemiologic Consideration**

The route of BK virus transmission has not been proven. One hypothesis is that transmission occurs via the respiratory or oral route. Documented serologic evidence exists of BK virus infection in correspondence with upper respiratory infection (Galan et al., 2005; Goudsmit, Wertheim-van Dillen, van Strien, & van der Noorda, 1982). Because of urinary shedding, oral transmission of BK virus may occur through ingestion of contaminated food or water (Sundsfjord et al., 1994). Organ transplantation and the transfusion of blood products also are possible transmission routes (Andrews, Shah, Daniel, Hirsch, & Rubin, 1988; Dolei et al., 2000).

Primary BK virus infection occurs during childhood—between the ages of four and five years on average (Knowles, 2001). Seroprevalence is at its lowest point after the loss of maternal antibodies at six months, but increases with age (Knowles). As many as 90% of adults worldwide may test positive for BK virus serology (Hirsch & Steiger, 2003). The primary site of BK virus infection is the reno-urinary tract, possibly because BK virus replication is host dependent. In addition, the reno-urinary tract provides an environment necessary for replication within the host. BK virus serologic evidence also exists for the renal cortex, lungs, ureters, bladder, prostate, and brain (Chesters, Hentage, & McCance, 1983; Goudsmit et al., 1982). However, as previously mentioned, BK virus usually remains asymptomatic in immunocompetent individuals.

**BK Virus in Hematopoietic Stem Cell Transplantation Recipients**

**Hemorrhagic Cystitis**

BK virus is found in a majority of patients after stem cell transplantation (Seber, Shu, Defor, Sencer, & Ramsey, 1999). Because most immunocompetent adults are BK virus seropositive,
a reactivation of BK virus in immunocompromised individuals is indicated. This reactivation is clinically linked with hemorrhagic cystitis in stem cell transplantation recipients. BK virus replicates in a stem cell transplantation recipient with a limited inflammatory response. During replication, cell lysis and necrosis occur, resulting in hemorrhagic cystitis and organ damage (Hirsch & Steiger, 2003).

Hemorrhagic cystitis occurs in about 7%–68% of stem cell transplantation recipients and varies in severity (Bedi et al., 1995) (see Table 2). Higher severity grades indicate increased mortality risk. Bladder irrigation or even cystectomy may be necessary to treat prolonged, high-grade hemorrhagic cystitis. In addition, hemorrhagic cystitis can be extremely painful for patients, and bladder perforation is a major concern.

Hemorrhagic cystitis can occur before and after engraftment. White blood cell engraftment occurs once neutrophil count recovers (absolute neutrophil count > 500 dl) and is maintained for at least 72 hours. Platelet engraftment occurs when a platelet count of more than 20 x 10^9 platelets/L is achieved and maintained for more than seven days. Platelet engraftment usually occurs later in the transplantation process than neutrophil engraftment. Hemorrhagic cystitis before engraftment occurs within 72 hours of a transplantation conditioning regimen (Yamamoto, Kusmi, & Kami, 2003) and often is referred to as early onset hemorrhagic cystitis. Hemorrhagic cystitis occurring before engraftment usually is related to an urethelial toxic conditioning regimen (Leung, Yuen, et al., 2005), including chemotherapy such as cyclophosphamide or irradiation. In fact, one of the most common etiologies of urothelial toxicity is acrolein, the metabolite of cyclophosphamide (Haselberger & Schwinghammer, 1995). Hemorrhagic cystitis is decreased when high-dose cyclophosphamide is given with mesna because mesna is able to bind to the acrolein and decrease the toxic effect (Schuchter, Hensley, Meropol, & Winer, 2002). Increased hydration and forced diuresis, with or without bladder irrigation, has been shown to significantly decrease the risk of hemorrhagic cystitis. The incidence of early onset hemorrhagic cystitis is about equal in autologous and allogeneic stem cell transplantation recipients (Leung et al., 2002), but usually is short-lived and less severe than hemorrhagic cystitis occurring after engraftment.

Hemorrhagic cystitis after engraftment usually is associated with BK virus reactivation that occurs with late onset (more than two weeks after transplantation) (Bedi et al., 1995). Late-onset hemorrhagic cystitis mostly occurs in allogeneic stem cell transplantation recipients (Leung et al., 2002). Contributing causes include prolonged hospitalization and poor quality of life. Late-onset hemorrhagic cystitis in this population usually is more severe, more difficult to control, and possibly life threatening.

BK virus replication and reactivation are host dependent and BK virus alone may not be enough to produce hemorrhagic cystitis. BK virus-associated hemorrhagic cystitis usually occurs around one month after neutrophil engraftment (Leung, Yuen, et al., 2005). The duration of BK virus-associated hemorrhagic cystitis can range from one week to more than four months (Leung, Yuen, et al.). The precise pathogenic relationship between BK virus and the development of late-onset hemorrhagic cystitis is unknown, but researchers believe that many risk factors play a role (Erard et al., 2004). Risk factors include conditioning regimen, donor type, graft-versus-host disease (GVHD), and BK viral load.

Risk Factors of BK Virus-Induced Hemorrhagic Cystitis

Conditioning Regimen

The conditioning regimen, or preparative regimen, is the chemotherapy and/or radiation given to a patient prior to hematopoetic stem cell transplantation. Conditioning regimens provide adequate immunosuppression to prevent rejection of the transplanted graft and to eradicate the disease for which the patient is being transplanted. Conditioning regimens are either myeloablative or nonmyeloablative. Myeloablative conditioning regimens are higher in

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
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<tbody>
<tr>
<td>I</td>
<td>Microscopic hematuria</td>
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<tr>
<td>II</td>
<td>Macroscopic hematuria</td>
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<tr>
<td>III</td>
<td>Macroscopic hematuria with clots</td>
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<tr>
<td>IV</td>
<td>Macroscopic hematuria instrumentation for evacuation of clots and/or renal dysfunction secondary to obstruction</td>
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Table 2. Hemorrhagic Cystitis Grading Scale

Note. Based on information from Erard et al., 2004.
intensity, carry a higher cell kill and immunosuppressive effect, and have higher toxicities. Nonmyeloblastic, or “reduced intensity” conditioning regimens, are less aggressive and have less toxicities than standard myeloblastic regimens. Nonmyeloblastic conditioning regimens often are used with older patients or patients who have comorbidities and decreased capacity to tolerate a fully myeloblastic regimen. The goal of a reduced intensity regimen is to produce decreased toxicity while providing an adequate anti-tumor effect (Slavin et al., 1998). Highly myeloblastic and nonmyeloblastic conditioning regimens are being used in stem cell transplantations. Conditioning regimen choices depend on the patient and his or her comorbidities, disease, cytogenetics, and prognostic factors. When examining BK virus-associated hemorrhagic cystitis, healthcare professionals should consider conditioning regimen intensity.

Giraud, Bogdanovic, and Priftakis (2006) examined the relationship between BK viruria and conditioning regimen intensity. Ninety allogenic stem cell transplantation recipients were studied; 44 received a reduced-intensity conditioning regimen and 46 received full myeloblastic conditioning. Fifteen of the 90 recipients (17%) developed hemorrhagic cystitis. The results demonstrated a statistically significant increase in hemorrhagic cystitis and BK viuria among patients who had received fully myeloblastic conditioning regimens (p < 0.01) (Giraud et al.). However, because of a lack of similar studies, more research is needed to support Giraud et al.’s findings.

Leung, Yuen, et al. (2005) suggested that myeloblastic conditioning regimens damage the urothelial lining and, as it regenerates, the lining may provide an environment that supports BK virus replication. Immunosuppression from the conditioning regimen also may add to BK virus replication (Leung, Yuen, et al.).

**Donor Type**

Late-onset hemorrhagic cystitis rarely occurs in autologous stem cell transplantation recipients (Leung et al., 2002), but an increased incidence of late-onset hemorrhagic cystitis in the allogenic population does exist. El-Zimaity et al. (2004) studied 105 patients with acute lymphoblastic leukemia who received allogenic stem cell transplantations and a 12 Gy total body irradiation-based conditioning regimen. El-Zimaity et al. examined the relationship between donor type and the development of late-onset hemorrhagic cystitis. Donor types included unrelated donor, unrelated cord blood, and matched related donor. A statistically significant increase in the development of late-onset hemorrhagic cystitis was found in the matched unrelated donor and unrelated cord blood groups (HR = 2.9, p = 0.04). In addition, 40% of the patients who had undergone unrelated cord blood transplantation also experienced hemorrhagic cystitis, although the authors did not include that information in their analysis secondary to the small sample size. Patients were not routinely tested for BK virus at the time of the study unless they were symptomatic. Of the patients who did develop late-onset hemorrhagic cystitis and were tested for BK virus, 59% were positive for BK viruria. Giraud et al. (2006) demonstrated that late-onset hemorrhagic cystitis occurs more frequently in unrelated donors.

A delayed immune recovery may be the key factor in the development of late-onset hemorrhagic cystitis in unrelated mismatched donors (Bogdanovic, Priftakis, Giraud, & Dallianis, 2006; El-Zimaity et al., 2004). In addition, unrelated donors tend to receive higher doses of immunosuppression for longer periods of time, providing a better opportunity for reactivation and replication of BK virus. Additional studies are needed to determine the correlation between degree of immunosuppression and BK virus reactivation and replication.

**Graft-Versus-Host Disease**

GVHD often occurs in patients who receive allogenic stem cell transplantation. Acute GVHD occurs in about 35%-50% of patients who undergo peripheral blood stem cell transplantation (Jacobsohn & Vogelsang, 2007). In essence, the donated stem cells attack the recipient’s body. Acute GVHD symptoms commonly manifest in the skin, gut, and liver, and acute GVHD is controlled with immunosuppressive agents. Acute GVHD occurs within 100 days of transplantation and can be mild to life threatening. Chronic GVHD occurs 100 days after transplantation and manifests in various organ systems.

Many alloimmune processes, such as acute GVHD, occur after allogenic transplantation and are believed to possibly contribute to development of BK viruria and hemorrhagic cystitis. Leung, Yeun, et al. (2005) suggested that donor lymphocytes may attack the uroepithelial cells during acute GVHD. Damage caused to the uroepithelial cells may provide an environment that supports BK virus replication and reactivation. In addition, patients experiencing acute GVHD also are prescribed one or more immunosuppressive agents. This decreases host immunity and may support an environment that enhances BK virus reactivation or replication. However, studies examining the relationship between late-onset hemorrhagic cystitis and acute GVHD are conflicting. Bedi et al. (1995) and Sencer, Haake, and Weisdorf (1993) found no true correlation between acute GVHD and late-onset hemorrhagic cystitis. However, Bogdanovic et al. (2004) conducted a pilot study of 31 allogenic stem cell transplantation recipients (18 children, 13 adults) that examined the relationship between hemorrhagic cystitis and BK viruria, viral load, acute GVHD, and conditioning regimen and found an association between high BK virus load in urine samples of patients with acute GVHD and the development of hemorrhagic cystitis. Because of the conflicting results, additional evaluations of acute GVHD as a risk factor for BK viruria and hemorrhagic cystitis are needed.

**BK Viral Load**

Increased BK viral load in plasma and urine correlate with hemorrhagic cystitis in stem cell transplantation recipients. Erard et al. (2005) examined BK viral load in plasma in relation to the development of hemorrhagic cystitis and demonstrated that hemorrhagic cystitis occurred more frequently with BK viral load of 10^7 copies/ml or higher. Azzi et al. (1999) and Leung et al. (2001) demonstrated that increased viral loads in urine correlate with clinical hemorrhagic cystitis. Leung et al. (2001) found that patients with 10^6–10^7 copies/ml did not develop hemorrhagic cystitis, but patients who had 10^7 copies/ml or higher did develop hemorrhagic cystitis. In addition, Wong et al. (2007) examined the relationship between *Polyoma* BK virus serologic levels before transplantation and BK viral reactivation after hematopoietic stem cell transplantation and found a strong association between positive BK virus serology prior to transplantation and the development of BK virus-associated
hemorrhagic cystitis after transplantation. Wong et al. helped demonstrate that BK virus serologic testing prior to transplantation may aid in identifying patients who are at increased risk of developing BK virus-associated hemorrhagic cystitis.

No set standard for BK virus screening exists; however, many stem cell transplantation centers are monitoring BK viral load weekly for the first 100 days after transplantation, when hemorrhagic cystitis is most likely to occur. Most centers are currently monitoring serum and urine BK viral loads. If an increase in BK viral load is noted, treatment can be initiated to prevent hemorrhagic cystitis development.

### Treatment of BK Virus-Associated Hemorrhagic Cystitis

Unfortunately, very little effective or standardized treatment exists for BK virus-associated hemorrhagic cystitis. The literature shows that cidofovir inhibits BK virus replication invitro and invivo (Leung, Chan, et al., 2005) and may be administered either IV or through bladder instillation. However, cidofovir is not used prophylactically because of its nephrotoxic and myelotoxic properties. Ciprofloxacin also demonstrates suppression of BK virus replication (Leung, Chan, et al., 2005) and, because it is not myelosuppressive, ciprofloxacin may be used prophylactically in stem cell transplantation recipients. Additional reported treatments for severe hemorrhagic cystitis include hyperbaric oxygen treatment, amifostine, factor VIII bladder irrigation or instillation, intramuscular vidarabine, and intravesical instillation of E-aminocaproic acid (Dememay et al., 2002; Hattori et al., 2001; Lakhani, Raptis, & Frame, 1999; Seabra et al., 2000; Srivastava et al., 1999). Cystectomy is an option for life-threatening cases (Koc et al., 2000), but it should be noted that BK virus is difficult to control even with these treatment modalities. BK virus can still cause damage in the kidney after a cystectomy. The treatments are not standardized for BK virus-associated hemorrhagic cystitis because of a lack of large patient population studies and a lack of high degrees of success. Outcomes often are poor and, therefore, safe and effective treatment of BK virus-induced hemorrhagic cystitis remains a challenge for clinicians.

### Nursing Considerations

When caring for patients with hemorrhagic cystitis, nurses must first rule out all other causes and sources of bleeding. Examples include gynecologic bleeding, disseminated intravascular coagulation, or septicemia-related bleeding. Tests to rule out calculi or tumor include urine microscopy, microbiologic cultures and cytology, platelet count and coagulation profile, and ultrasound or radiologic studies (Leung, Chan, et al., 2005). The onset of the hemorrhagic cystitis also must be considered. An early presentation is likely related to the conditioning regimen. The probability increases that the hematuria is linked to BK virus-associated hemorrhagic cystitis if it occurs as late-onset hemorrhagic cystitis. Blood and urine should be tested for BK virus. Once an official diagnosis is made, supportive treatment such as aggressive IV hydration should begin. A urology consultation should be obtained if the patient presents with severe hemorrhagic cystitis. Manual or continuous bladder irrigation may be necessary if a clot obstruction develops. A nephrology consultation also should be considered if renal dysfunction occurs. Hemoglobin, hematocrit, and platelet count should be monitored closely. Supportive blood product transfusions should be conducted as needed. Patients often experience a great deal of pain and an analgesia, with or without opioid, may be necessary. If the patient requires continuous bladder irrigation for long periods of time, life-threatening bladder perforation may occur.

Patients often become frustrated and depressed as they experience hemorrhagic cystitis, particularly patients who do not show clinical improvement despite treatment efforts. A referral to a social worker or psychologist may be necessary.

### Summary

BK virus is a causative factor in the development of late-onset hemorrhagic cystitis in stem cell transplantation recipients and can be life threatening in severe cases. Patients often experience poor quality of life with prolonged hospitalization. Despite numerous advances in stem cell transplantation methods, BK virus-associated hemorrhagic cystitis still is a troubling issue for healthcare providers. The exact pathology between the virus and the development of BK virus-associated hemorrhagic cystitis is unclear. Possible risk factors include conditioning regimen, donor type, acute GVHD, and viral load. No standardized treatment exists at this time and current modalities do not provide high degrees of success. Additional research is needed to overcome this virus-related condition.

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The author gratefully acknowledges Cheryl Tompkins, CRNP, Margaret Rosenzweig, CRNP, Sherri Miller, APN, Marcus Mapara, MD, Mouzner Agha, MD, Anastasios Raptis, MD, and David Weber, MD, for their help and support.

### References


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