

NEPHROLOGY

Rounds®

AS PRESENTED IN THE ROUNDS OF
THE NEPHROLOGY DIVISION OF
BRIGHAM AND WOMEN'S HOSPITAL
BOSTON, MASSACHUSETTS

BK Virus Nephropathy: A Challenging Complication in Kidney Transplant Recipients

By WAICHI WONG, MD, and ANIL CHANDRAKER, MBCHB

In the past decade, BK virus (BKV), a human polyomavirus, has been recognized as an increasing cause of severe kidney allograft dysfunction. This growing incidence correlates with the use of more potent immunosuppressant medications. The prevalence of a BKV nephropathy (BKVN) ranges from 1% to 10%.¹ In turn, more than 50% of the cases result in allograft loss.² The diagnosis of allograft dysfunction is based on a combination of the presence of urinary decoy cells, virus in the urine or blood, and histological findings on kidney biopsy. The current treatment of BKVN consists of a reduction in immunosuppressant therapy, since universally, antiviral therapy with cidofovir or leflunomide has yielded poor results. Early diagnosis of BKV infection is essential, and in recent years, the combination of early detection, prompt diagnosis, and appropriate reduction in immunosuppressant therapy has been associated with better outcomes.

Kidney transplant recipients (KTRs) receive lifelong immunosuppressant medications, which puts them at increased risk of infections.³ BKVN is emerging as a significant infectious complication. The terminology "BK virus" originated in 1971 from a KTR with initials BK who had a urethral stricture and in whose urine the virus was first detected.⁴ During the cyclosporine-prednisone era of the 1980s and early 1990s, there were no reported cases until Purigalla et al⁵ observed their first case in 1995. Subsequently, there has been a surge of BKVN cases in transplant centers in the United States (US) and around the world. It is still unclear which key factors are behind this growing incidence. One potential explanation is that the introduction of more potent immunosuppressive agents such as tacrolimus, mycophenolate mofetil (MMF), and antilymphocyte globulins, result in overimmunosuppression and permissiveness for BKVN.² The growing numbers, coupled with the lack of a definitive treatment, pose a threat to long-term graft survival.³

Virology

BKV is a double-stranded deoxyribonucleic acid (DNA) human polyomavirus with a 5300-base pair genome that replicates in the host nucleus.⁶ The polyoma family includes JC virus (the well-known cause of progressive multifocal leukoencephalopathy), simian virus SV40, and monkey polyomavirus. The BKV genome shares an overall homology of 75% with the JC virus and 70% with SV40; it can be divided into regulatory, early, and late regions. The regulatory section of the BKV genome is the noncoding control region (NCCR), the early-coding region is responsible for the small and large T antigens (T-ag), and the late-coding region is responsible for three capsid proteins, viral protein (VP1, VP2, and VP3) and agnoprotein.⁷ The NCCR contains the promoter/enhancer elements of early and late genes, and initiates replication. Early genes encode the large tumor antigen (LT-ag) as the regulatory master protein and the supporting small T-ag.⁸ Late gene expression is initiated after viral DNA replication has started. After translation into the cytoplasm, the viral capsids are transported to the nucleus for virion assembly supported by the agnoprotein.⁸

Transmission and reactivation

Several serological studies suggest that primary BKV infection occurs during childhood at a median age of 4-5 years.⁹ Seroprevalence is at its lowest at age 6 months after the loss of maternal antibodies, and increases to about 75% among adults worldwide (range 46%-94%).¹⁰ After the initial infection, BKV persists in the uroepithelium. It is postulated that during kidney transplantation, there is viremic spread from the site of entry; subsequently, the virus



BRIGHAM AND
WOMEN'S HOSPITAL



HARVARD
MEDICAL SCHOOL
TEACHING AFFILIATE

Co-Editors

Joseph V. Bonventre, M.D., Ph.D.,
(Division Director)

Barry M. Brenner, M.D., F.R.C.P.,
(Director Emeritus)

Nephrology Division Brigham and Women's Hospital

Reza Abdi, M.D.
Jessamyn Bagley, Ph.D.
Sangeeta Bhattia, M.D., Ph.D.
Joseph V. Bonventre, M.D., Ph.D.
Barry M. Brenner, M.D.
Steven Brunelli, M.D.
Anil K. Chandraker, M.B., M.R.C.P.
David M. Charytan, M.D.
Mary Choi, M.D.
Kenneth B. Christopher, M.D.
Gary C. Curhan, M.D., Sc.D.
Bradley M. Denker, M.D.
Jeremy Duffield, M.D., Ph.D.
John P. Forman, M.D.
Markus H. Frank, M.D.
Monica Grafals, M.D.
Indira Guleria, Ph.D.
Dirk M. Hentschel, M.D.
Andreas Herrlich, M.D., Ph.D.
Li-Li Hsiao, M.D., Ph.D.
Benjamin D. Humphreys, M.D., Ph.D.
John J. Iacomini, Ph.D.
Takaharu Ichimura, Ph.D.
Vicki Rubin Kelley, Ph.D.
Julie Lin, M.D., M.P.H.
Edgar L. Milford, M.D.
David B. Mount, M.D.
Nader Najafian, M.D.
Shona Pendse, M.D.
Martin R. Pollak, M.D.
Mohamed H. Sayegh, M.D.
Julian L. Seifter, M.D.
Jagesh V. Shah, Ph.D.
Alice M. Sheridan, M.D.
Ajay K. Singh, M.B., M.R.C.P. (U.K.)
Theodore I. Steinman, M.D.
Eric N. Taylor, M.D.
John K. Tucker, M.D.
Takuya Ueno, M.D., Ph.D.
Vishal Vaidya, Ph.D.
Sushrut S. Waikar, M.D.
Wolfgang C. Winkelmayer, M.D., Sc.D.
Xueli Yuan, M.D., Ph.D.
Kambiz Zandi-Nejad, M.D.
Jing Zhou, M.D., Ph.D.

Brigham and Women's Hospital

Website: www.brighamandwomens.org/renal

The editorial content of *Nephrology Rounds* is determined solely by the Nephrology Division of Brigham and Women's Hospital.

**Nephrology Rounds is approved
by the Harvard Medical School
Department of Continuing Education
to offer continuing education credit**

is presumed to enter the renal cortex through the renal peritubular capillaries.¹¹

Interestingly, the exact pathogenesis of BKV infection leading to BKVN is unclear. Hypothetical mechanisms include the source of BKV; immunological factors such as host humoral and cellular immunity, alloimmune activation and immunosuppression medications, kidney specificity such as ischemic injury, and viral virulence.¹²

The nature of BKV transmission is also poorly understood, but is presumed to be respiratory. There is serological evidence of primary respiratory infection, which suggests transmission through aerosol or fomites.¹³ Urinary shedding argues for oral transmission by contaminated food or water. BKV is highly resistant to environmental inactivation; it has been detected in human sewage and shellfish samples around the world. Other potential routes include blood, semen, and organ transplantation.¹⁴ Transplacental transmission of polyomavirus has been suggested based on the detection of immunoglobulin M (IgM) in cord blood samples, but this remains controversial.¹⁵

The most frequent primary symptoms associated with BKV infections are upper respiratory infection as well as sporadic reports of acute cystitis, with or without hematuria.¹⁶ As the primary infection resolves, the virus enters a latency phase in the uroepithelium.¹⁷ BKV disease caused by reactivation of the latent virus is normally not seen in the immunocompetent host. There is an intermittent low-level replication of BKV viruria occurring in 5% of healthy individuals. BKV disease in itself is rare, which suggests that additional factors are needed for the disease to develop, such as changes in immune status. Reactivation of latent viruses has been reported in old age, pregnancy, and diabetes mellitus, as well as in immunosuppression associated with organ transplantation or human immunodeficiency virus (HIV) infection.¹⁶ Such conditions can lead to transient, asymptomatic and self-limiting viral activation, especially in the urothelium.¹⁶ In KTRs, there is progressive replication leading to BKVN.

Risk factors for BKV infection

There are conflicting reports regarding risk factors for BKVN in KTRs, since it may be donor or recipient related.¹⁸ Recipient-related risk factors include older age, male gender, Caucasian race, diabetes mellitus, acute rejection, and total human leukocyte antigen mismatches.¹⁶ Donor-related risk factors include presence of active BKV or cytomegalovirus, deceased-donor transplantation, and organ cold ischemia time.¹⁹

Moreover, there is no doubt that immunosuppression has the greatest impact. In the last 10 years, since introducing the third generation of immunosuppressant medications (eg, tacrolimus and MMF) the prevalence of BKVN has increased.^{2,20} Recent trials comparing tacrolimus versus cyclosporine demonstrated no significant difference in development of BKVN as well as with MMF and BKVN development.^{21,22} It seems reasonable to infer that it is the maintenance of higher doses of medications rather than the presence of any particular agent that

increases the risk of BKVN. In addition, steroid pulses and antilymphocyte globulins used for cellular rejection have been noted to increase the risk of BKVN.²³

Outcomes

BKV reactivation, specifically in KTRs, can cause 3 different lesions: hemorrhagic cystitis, urethral stenosis, and interstitial nephritis.²⁴ Sachdeva et al²⁵ reported that BKVN has been diagnosed as early as 6 days and as late as 6 years post-transplant. Reactivation of BKV in KTRs can vary up to 50% in prevalence for the first year post-transplantation.¹⁶ Unfortunately, the most common clinical feature is the *lack* of signs and symptoms of infection. BKVN can vary from normal creatinine (early stages) to markedly elevated creatinine (late stages with severe injury). However, BKVN is often not clinically considered until there is elevated creatinine. In recent years, routine post-transplant protocol biopsy has also detected BKVN in the absence of serum creatinine elevation.¹² Current reports suggest the prevalence of BKVN ranges from 1% to 10%.¹ Progressive renal failure with graft loss from BKVN ranges from 10% to >80% of the cases.¹⁶ Rare fatal disseminated BKV infection just after deceased donor transplantation has also been reported.¹²

The clinical course of KTRs with BKVN is varied, and the reduction of viral load does not always translate into improved graft function, owing to the irreversible chronic allograft changes. Some suggest that those KTRs with BKVN have better graft outcomes with earlier diagnosis (less interstitial and tubular damage on kidney biopsy).^{26,27} Vasudev et al¹⁸ report that a serum creatinine level >2.2 mg/dL at the time of diagnosis of BKVN correlates with prolonged graft survival. Recently published series suggest that histological features such as moderate to severe fibrosis indicate poor outcomes.¹⁶

Diagnosis

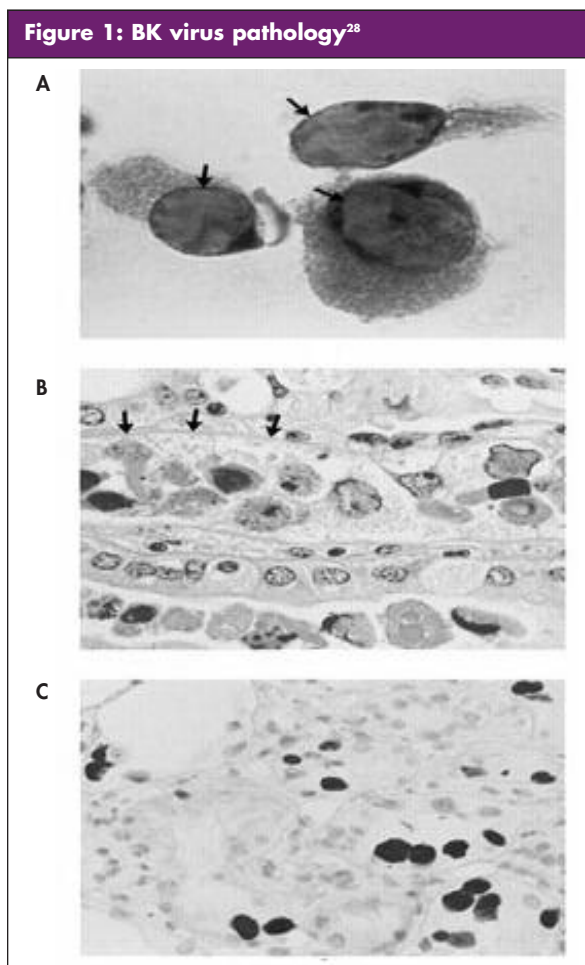
Given the high prevalence of graft loss, it is imperative to make an early and appropriate diagnosis. Currently, there are several available modalities for laboratory monitoring of BKV infection (Table 1).¹²

Cytology. Infected cells in the urine, known as decoy cells, show rounded nuclei which are generally larger than the average transitional and tubular cell. Using a Papanicolaou-stain thin prep smear, the nuclei appear to have viral inclusions with dense granular basophilic cytoplasm with no surrounding halo (Figure 1A).²⁸ Hirsch et al²⁹ reported that the positive predictive value of decoy cells for BKVN was 25%-30%, but the negative predictive value was greater than 99%. Thus, the presence of decoy cells in KTRs implies BKV reactivation and not necessarily BKVN. This is a simple, quick, and inexpensive screening tool, but is limited with respect to predictive value.

Serology. Recently, polymerase chain reaction (PCR) assay has been used as a more sensitive method of detecting BKV viral load. Urine PCR has a higher sensitivity but lower specificity than urine cytology and therefore is not routinely used for BKVN diagnosis.³⁰

Table 1: Diagnosis of BK virus nephropathy		
Tests	Findings	Comments
Urine cytology	Presence of decoy cells	Seen in 40%-60% of transplant recipients, good screening test, positive predictive values ~20%
Viremia (plasma BKV DNA)	Copies >7000 per mL plasma values	Seen in 10%-20% of transplant recipients, good screening test, positive predictive values ~60%
Viruria (urinary BKV DNA)	Copies 100-fold higher than plasma values	Seen in 30%-40% of transplant recipients, good screening test, positive predictive values ~40%
Urinary BKV mRNA (active viral replication)	Copies diagnostic of BKVN	To be confirmed in other studies, research tool
BKV DNA in renal tissue	Detection of BKV DNA in renal biopsy tissue	Negative predictive value 100%, positive predictive values ~70%
BKV DNA in renal tissue	Inflammatory changes with viral cytopathic effects, positive immunoperoxidase reaction with SV40 stain, predominant CD20-positive lymphocytic infiltrates	Gold standard, invasive procedure, focal lesions, chronic state with minimal viral cytopathic effects. Mimics acute rejection.
Serum BKV-specific antibodies	Diagnostic levels of IgM and IgG?	Seen in 80%-90% of general population
BKV-specific antibodies and BKV DNA	Diagnostic levels of BKV-specific antibodies IgM, IgG, and BKV DNA?	Research tool
T-cell immunity	Diagnostic measurement?	Research tool

BKVN = BK virus nephropathy; DNA = deoxyribonucleic acid; Ig = immunoglobulin
Adapted by permission from Macmillan Publishers Ltd: Hariharan S. *Kidney Int.* 2006;69(4):655-662. Copyright © 2006.



A: Decoy cells in urine (PAP, x400). **B:** Renal tubules w/epithelial cells containing viral inclusions (H&E, x160). **C:** Immunohistological stain shows nuclei of the epithelial cells of the tubules (confirms BKV) (mouse monoclonal Ab, x100). Copyright © 2000. Massachusetts Medical Society.

Ding et al³¹ proposed measuring messenger ribonucleic acid for BKV capsid protein VP1 in urine with specificity and sensitivity as high as 93.8% and 93.9%, respectively. However, this method is not yet in routine use.

On the other hand, serum PCR analysis of BKV has become a reliable method of predicting BKV infection with a positive predictive value of 50% and negative predictive value of 100%.²⁸ Hirsch et al⁶ reported that circulating plasma BKV DNA of > 10 000 copies/mL correlates with acute BKVN. Of note, PCR assays are not standardized and interlaboratory variability can exceed 1 log₁₀.

Histology:

The gold standard for BKVN diagnosis requires a kidney biopsy and demonstration of BKV inclusions in tubular epithelial or Bowman capsular epithelial cells.³¹ BKV infection is accompanied by varying degrees of inflammatory cell infiltrates, tubular atrophy, and fibrosis (Figure 1B).²⁷ BKVN progresses through 3 stages, each with a different histological pattern:^{5,15}

- **Stage A:** Viral activation, identified by positive intranuclear immunohistochemical or *in situ* hybridization signals, is noted in cortical or medullary tubular cross-sections. Interstitial inflammation is absent or minimal. Interstitial fibrosis and tubular atrophy do not affect >10% of the biopsy core. If diagnosed at this stage, BKV responds to therapy and typically results in favorable long-term graft survival.
- **Stage B:** Viral activation is seen in cortical and medullary tubular cross-sections with conspicuous virally induced epithelial cell lysis, denudation of tubular basement membrane, and interstitial edema. There are significant mononuclear inflammatory cell infiltrates, but interstitial fibrosis and tubular atrophy are <50%.

Table 2: Treatment of BK virus nephropathy

	Mode of of action	Comments
Cidofovir	Antiviral	Nephrotoxicity, potential benefit with reduction in immunosuppression. Needs evaluation.
Leflunomide	Antiviral	Potential clinical efficacy with therapeutic trough level (50-100 g/mL) with reduction in immunosuppression
Fluoroquinolones	Antiviral?	Seem to inhibit BK viral replication <i>in vitro</i>
Intravenous immunoglobulin	Augments immunity	Efficacy unknown
Reduction, discontinuation, and/or change in immunosuppressive agents (MMF, tacrolimus, cyclosporine, sirolimus, prednisone)	Decreasing immunosuppression	Safe and appears effective, risk of acute rejection in selected recipients with immunosuppressive alterations
Prevention: monitoring viral disease (urinary decoy cells, viremia, viruria, and surveillance biopsy) and altering immunosuppression	Diagnosis of preclinical, subclinical, or early nephritis	Safe and effective with proper monitoring, risk of acute rejection with immunosuppressive alterations

MMF = mycophenolate mofetil

Adapted by permission from Macmillan Publishers Ltd: Hariharan S. *Kidney Int.* 2006;69(4):655-662. Copyright © 2006.

- **Stage C:** Viral replication is associated with tubular epithelial injury. Fibrosis and tubular atrophy affect >50% of the biopsy sample. The fibrosis noted in stage C is irreversible and correlates with graft loss.

The cytopathic effects seen by light microscopy are typical, but not pathognomonic for BKVN. Confirmatory immunohistochemistry or *in situ* hybridization studies are usually performed using antibodies against specific BKV proteins or probes complementary to viral DNA (Figure 1C).²⁸ Hirsh et al³² have also argued that immunohistochemistry using antibodies against the large T antigen of SV40 increases the sensitivity and specificity of the diagnosis of BKVN. Electron microscopy can demonstrate unenveloped, viral particles, approximately 40 nm in diameter. It is important to note that BKVN can be focal in distribution and diagnosis can be missed by sampling error. Therefore, ideally >2 cores should be examined. If the biopsy is negative but there is associated BKV viremia with allograft dysfunction, a presumptive diagnosis of BKVN should be considered.

Given the growing incidence and difficulty of treating BKVN, it is important to develop a cost-effective screening tool. Buehrig et al²⁶ have diagnosed BKVN early in protocol surveillance biopsies of stable allografts with favorable outcomes. Many in the field of transplantation are advocates for protocol biopsies, but often it is not logistically feasible or it is not perceived to be cost-effective. Randhawa and Brennan³³ suggested a BK monitoring algorithm that is cost-effective if the incidence of BKVN in a transplant program exceeds 2.1%. The screening cost substantially offsets the savings related to reductions in immunosuppression following BKVN diagnosis.

The histological features of BKVN may mimic those of acute cellular rejection, or both processes may be present concurrently. It is important to establish the difference between the two, since the appro-

prate therapy for BKVN is a reduction, rather than an increase, of immunosuppression. The use of tubular major histocompatibility complex class II (human leukocyte antigen DR) or complement C4 fragment d (C4d) along peritubular capillaries is an easy way of distinguishing acute rejection from BKVN.¹⁶ Definitive diagnosis of rejection concurrent with viral nephropathy should only be made if endarteritis, fibronecrosis, arterial necrosis, glomerulitis, or accumulation of complement degradation product C4d along the peritubular capillaries is observed.¹⁶

Treatment

Management of BKV infection should target virus elimination, acute rejection avoidance, and preservation of kidney function. Current treatment of BKVN is inadequate as there are no uniformly effective antiviral agents currently available. Prevention of BKVN seems to be a better strategy. In a large study, Brennan et al²² demonstrated that prospective monitoring of urine and blood for BKV and pre-emptive withdrawal of the antimetabolite upon development of viremia resulted in clearance of viremia and viruria; this appeared to decrease the risk of BKVN without increasing the risk of acute rejection. Bressollette-Bodin et al³⁴ also found that viremia and viruria could decrease over time with standard immunosuppressant reductions without pre-emptive complete withdrawal of any component of the immunosuppression regimen. The primary treatment of BKVN is reduction of immunosuppression. In practice, primary interventions include decreasing or stopping the antimetabolite such as MMF while simultaneously lowering the calcineurin inhibitor trough levels. The switch from tacrolimus to cyclosporine or cyclosporine to sirolimus has been reported to decrease risk of BKVN.¹⁸ Care must be taken because rapid reduction in immunosuppression may result in insufficient control of immunity and places the graft at risk of acute rejection.

In KTRs with BKVN and progressive graft dysfunction, it is unlikely they will respond to reduction in immunosuppression alone; the addition of antivirals should be considered (Table 2).¹² Antiviral drugs such as acyclovir, ganciclovir, foscarnet, and ribavirin have not demonstrated an effect on BKVN. There were some initial case reports implicating a role for amantadine and vidaribine, but subsequent studies have revealed no benefit in treating BKVN.¹² Other antiviral agents used with anecdotal success include cidofovir, leflunomide, fluoroquinolones, and intravenous gammaglobulin.³⁵⁻⁴¹ The efficacy of each of these strategies is unclear, since there was a concomitant immunosuppression reduction in each case.

Cidofovir is a cytosine nucleoside analog that inhibits viral DNA synthesis and has mainly been used to treat cytomegalovirus retinitis in HIV-infected patients. It has *in vitro* activity against papovaviruses (including polyomavirus), adenoviruses, herpesviruses, iridoviruses and poxviruses. It has also been used in the treatment of BKVN. A recent report indicated a favorable effect on BKVN with low-dose cidofovir (0.25-1 mg/kg per dose without probenecid) every 1 to 3 weeks.³⁵ However, the nephrotoxicity of cidofovir limits its use.

Leflunomide, metabolized to its active metabolite A771726, inhibits pyrimidine synthesis; the inhibitory effects on protein phosphorylation is presumed to provide some of the antiviral effects. It is used mainly to treat rheumatoid arthritis. Williams et al³⁶ and Josephson et al³⁷ both reported stabilization or improvement in serum creatinine and reduction of viral load in BKVN patients treated with leflunomide.

Fluoroquinolone antibiotics seem to inhibit BKV replications *in vitro*. Recently, 5 fluoroquinolones (gatifloxacin, ofloxacin, ciprofloxacin, trovafloxacin, and levofloxacin) were examined and proved to be able to inhibit viral replication of SV40 in permissive monkey cells.^{38,39} Chandraker et al⁴⁰ found a positive effect with a short course of gatifloxacin (500 mg orally once daily) in KTRs excreting BKV in urine.

Intravenous immunoglobulin (IVIG) is used to treat immunodeficient patients such as those with autoimmune or inflammatory diseases. In KTRs, it has been used to treat steroid-resistant rejection, in desensitization protocols, and as a maintenance immunosuppressant. The mechanism of action of IVIG is complex; it transcends antibody transference, including modulation and expression of Fc receptors, inhibition of complement-mediated damage, and interference with the inflammatory cytokines network. In theory, the immunomodulatory effects of IVIG may neutralize the antibodies against BKV. There are several reports on the treatment of BKVN patients with IVIG showing limited success.⁴¹

All these proposed antiviral therapies require prospective randomized controlled studies to evaluate their efficacy.

Retransplantation

Successful repeat kidney transplantation with graft loss caused by BKVN can be safely performed. A pooled study of 5 US centers revealed that successful retransplantation can be performed without recurrence in 90% of cases, with a mean follow-up of over 2 years; the risk of recurrence does not seem to be increased in comparison with the first graft.⁴² Womer et al⁴³ reported successful pre-emptive re-transplantation with simultaneous allograft nephrectomy in 2 patients with active BKVN and viremia at the time of surgery. In essence, intense immunosuppression of KTRs with retransplantation due to BKVN should be avoided. Ideally, post-transplant, BK viral load should be as low as possible. The risk of BKVN after a second transplant is low, but should not be ignored.

Conclusion

BKVN is becoming an increasingly significant complication after kidney transplantation. Once it is diagnosed, there are limited improvements in graft survival and no optimal antiviral treatment. The pathogenesis of BKV in KTRs requires further investigation. Currently, the mainstay for graft survival is early diagnosis, prevention of BKVN, and cautious pre-emptive reduction in the patient's immunosuppression regimen. Until a safe antiviral agent becomes available, reduction in immunosuppression appears to be the best partial treatment for BKVN.

References

- Hirsch HH, Brennan DC, Drachenberg CB, et al. Polyomavirus-associated nephropathy in renal transplantation: interdisciplinary analyses and recommendations. *Transplantation*. 2005;79(10):1277-1282.
- Binet I, Nicleleit V, Hirsch HH, et al. Polyomavirus disease under new immunosuppressive drugs: a cause of renal graft dysfunction and graft loss. *Transplantation*. 1999;67(6):918-922.
- Hirsch HH, Knowles W, Dickenmann M, et al. Prospective study of polyomavirus type BK replication and nephropathy in renal-transplant recipients. *N Engl J Med*. 2002;347(7):488-496.
- Gardner SD, Field AM, Coleman DV, Hulme B. New human papovavirus (B.K.) isolated from urine after renal transplantation. *Lancet*. 1971; 19(7712):1253-1257.
- Purighalla R, Shapiro R, McCauley J, Randhawa P. BK virus infection in a kidney allograft diagnosed by needle biopsy. *Am J Kidney Dis*. 1995;26(4): 671-673.
- Hirsch HH, Steiger J. Polyomavirus BK. *Lancet Infect Dis*. 2003;3(10):611-623.
- Moret H, Ingrand D. Les polyomavirus humains. *Médecine Thérapeutique*. 1997;6:473-476.
- Rubinstein R, Pare N, Harley EH. Structure and function of the transcriptional control region of nonpassaged BK virus. *J Virol*. 1987;61(5):1747-1750.
- Shah KV, Daniel R, Warszawski R. High prevalence of antibodies to BK virus, an SV40-related papovavirus, in residents of Maryland. *J Infect Dis*. 1973;128(6):784-787.
- Knowles WA. The epidemiology of BK virus and the occurrence of antigenic and genomic subtypes. In: Khalili K, Stoner GL (eds). *Human Polyomaviruses: Molecular and Clinical Perspectives*, New York: Wiley-Liss; 2001: 527-559.
- Zambrano A, Kalantari M, Simoneau A, Jensen JL, Villarreal LP. Detection of human polyomaviruses and papillomaviruses in prostatic tissue reveals the prostate as a habitat for multiple viral infections. *Prostate*. 2002;53: 263-276.
- Hariharan S. BK virus nephritis after renal transplantation. *Kidney Int*. 2006; 69(4):655-662.
- Goudsmit J, Wertheim-van Dillen P, van Strien A, van der Noordaa J. The role of BK virus in acute respiratory tract disease and the presence of BKV DNA in tonsils. *J Med Virol*. 1982;10(2):91-99.

14. Andrews CA, Shah KV, Daniel RW, Hirsch MS, Rubin RH. A serological investigation of BK virus and JC virus infections in recipients of renal allografts. *J Infect Dis.* 1988;158(1):176-181.

15. Pietropaolo V, Di Taranto C, Degener AM, et al. Transplacental transmission of human polyomavirus BK. *J Med Virol.* 1998;56(4):372-376.

16. Bonvoisin C, Weekers L, Xhignesse P, Grosch S, Milicevic M, Krzesinski JM. Polyomavirus in renal transplantation: a hot problem. *Transplantation.* 2008;85(7 Suppl):S42-48.

17. Boubenider S, Hiesse C, Marchand S, Hafi A, Kriaa F, Charpentier B. Post transplantation polyomavirus infection. *J Nephrol.* 1999;12(1):24-29.

18. Ginevri F, De Santis R, Comoli P, et al. Polyomavirus BK infection in pediatric kidney-allograft recipients: a single analysis of incidence, risk factors, and novel therapeutic approaches. *Transplantation.* 2003;75(8):1266-1270.

19. Vasudev B, Hariharan S, Hussain SA, Zhu YR, Bresnahan BA, Cohen EP. BK virus nephritis: risk factors, timing and outcomes in renal transplant recipients. *Kidney Int.* 2005;68(4):1834-1839.

20. Mengel M, Marwedel M, Radermacher J, et al. Incidence of polyomavirus-nephropathy in renal allografts: influence of modern immunosuppressive drugs. *Nephrol Dial Transplant.* 2003;18(6):1190-1196.

21. Lopez-Rocafort L, Wang C, Miller B. A prospective evaluation of BK virus infection in renal transplant patients [Abstract]. *Am J Transplant.* 2002;2:S260.

22. Brennan DC, Agha I, Bohl DL, et al. Incidence of BK with tacrolimus versus cyclosporine and impact of preemptive immunosuppression reduction. *Am J Transplant.* 2005;5(3):582-594.

23. Moens V, Subramaniam N, Johansen B, Johansen T, Traavik T. A steroid hormone response unit in the late leader of the noncoding control region of the human polyomavirus BK confers enhanced host cell permissivity. *J Virol.* 1994;68(4):2398-2408.

24. Colvin RB, Mauyyedi S. Differential diagnosis between infection and rejection in renal allografts. *Transplant Proc.* 2001;33(1-2):1778-1779.

25. Sachdeva M, Nada R, Jha V, Sakhuja V, Joshi K. The high incidence of BK polyoma virus infection among renal transplant recipients in India. *Transplantation.* 2004;77(3):429-431.

26. Buehrig CK, Lager DJ, Stegall MD, et al. Influence of surveillance renal allograft biopsy on diagnosis and prognosis of polyomavirus-associated nephropathy. *Kidney Int.* 2003;64(2):665-673.

27. Drachenberg CB, Papadimitriou JC, Wali R, et al. Improved outcome of polyoma virus allograft nephropathy with early biopsy. *Transplant Proc.* 2004;36(3):758-759.

28. Nickeleit V, Klimkait T, Binet IF, et al. Testing for polyomavirus type BK DNA in plasma to identify renal-allograft recipients with viral nephropathy. *N Engl J Med.* 2000;342(18):1309-1315.

29. Nickeleit V, Hirsch HH, Binet IF, et al. Polyomavirus infection of renal allograft recipients: from latent infection to manifest disease. *J Am Soc Nephrol.* 1999;10(5):1080-1089.

30. Holman CJ, Van Burik JA, Hinrichs SH, Balfour HH Jr. Specific detection of human BK polyomavirus in urine samples of immunocompromised patients. *Clin Diagn Lab Immunol.* 2003;10(1):66-69.

31. Ding R, Medeiros M, Dadhania D, et al. Non invasive diagnosis of BK virus nephritis by measurement of messenger RNA for BK VP1 in urine. *Transplantation.* 2002;74(7):987-994.

32. Hirsch HH. Polyomavirus BK nephropathy: a (re-)emerging complication in renal transplantation. *Am J Transplant.* 2002;2(1):25-30.

33. Randhawa P, Brennan DC. BK virus infection in transplant recipients: an overview and update. *Am J Transplant.* 2006;6(9):2000-2005.

34. Bressollette-Bodin C, Coste-Burel M, Hourmant M, Sebille V, Andre-Garnier E, Imbert-Marcille BM. A prospective longitudinal study of BK virus infection in 104 renal transplant recipients. *Am J Transplant.* 2005;5(8):1926-1933.

35. Araya CE, Lew JF, Fennel RS 3rd, Neiberger RE, Dharnidharka VR. Intermediate-dose cidofovir without probenecid in the treatment of BK virus allograft nephropathy. *Pediatr Transplant.* 2006;10(1):32-37.

36. Williams JW, Javaid B, Kadambi PV, et al. Lefunomide for polyomavirus type BK nephropathy. *N Engl J Med.* 2005;352(11):1157-1158.

37. Josephson MA, Gillen D, Javaid B, et al. Treatment of renal allograft polyoma BK virus infection with leflunomide. *Transplantation.* 2006;81(5):704-710.

38. Randhawa PS. Anti-BK virus activity of ciprofloxacin and related antibiotics. *Clin Infect Dis.* 2005;41(9):1366-1367.

39. Ali S, Chandraker A, Decaprio J. Inhibition of polyoma helicase activity by quinolones. *J Am Soc Nephrol.* 2003;14:43A.

40. Chandraker A, Ali S, Drachenberg CB, et al. Use of fluoroquinolones to treat BK infection in renal transplant recipients [abstract]. *Am J Transplant.* 2004;4(suppl 8):587.

41. Sener A, House AA, Jevnikar AM, et al. Intravenous immunoglobulin as a treatment for BK virus associated nephropathy: one-year follow-up of renal allograft recipients. *Transplantation.* 2006;81(1):117-120.

42. Ramos E, Vincenti F, Lu WX, et al. Retransplantation in patients with graft loss caused by polyoma virus nephropathy. *Transplantation.* 2004;77(1):131-133.

43. Womer KL, Meier-Kriesche HU, Bucci CM, et al. Pre-emptive retransplantation for BK virus nephropathy: successful outcome despite active viremia. *Am J Transplant.* 2006;6(1):209-213.

Abstract of Interest

Presence of Urinary Haufen Accurately Predicts Polyomavirus Nephropathy

SINGH HK, ANDREONI KA, MADDEN V, TRUE K, DETWILER R, WECK K, NICKELEIT V.

There are no accurate, noninvasive tests to diagnose BK polyomavirus nephropathy, a common infectious complication after renal transplantation. This study evaluated whether the qualitative detection of cast-like, three-dimensional polyomavirus aggregates (“Haufen”) in the urine accurately predicts BK polyomavirus nephropathy. Using negative-staining electron microscopy, we sought Haufen in 194 urine samples from 139 control patients and in 143 samples from 21 patients with BK polyomavirus nephropathy. Haufen detection was correlated with pathology in concomitant renal biopsies and BK viremia (decoy cell shedding and viral load assessments by PCR) and BK viremia (viral load assessments by PCR). Haufen originated from renal tubules containing virally lysed cells, and the detection of Haufen in the urine correlated tightly with biopsy confirmed BK polyomavirus nephropathy (concordance rate 99%). A total of 77 of 143 urine samples from 21 of 21 patients with BK polyomavirus nephropathy (disease stages A-C) contained Haufen, and during follow-up (3 to 120 wk), their presence or absence closely mirrored the course of renal disease. All controls were Haufen-negative, however, high viremia or viruria were detected in 8% and 41% of control samples, respectively. kappa statistics showed fair to good agreement of viruria and viremia with BK polyomavirus nephropathy or with Haufen shedding and demonstrated an excellent agreement between Haufen and polyomavirus nephropathy (kappa 0.98). Positive and negative predictive values of Haufen for BK polyomavirus nephropathy were 97% and 100%, respectively. This study shows that shedding of urinary Haufen and not BK viremia and viruria accurately mark BK polyomavirus nephropathy. It suggests that the detection of Haufen may serve as a noninvasive means to diagnose BK polyomavirus nephropathy in the urine.

J Am Soc Nephrol. 2009 Feb;20(2):416-27. Epub 2009 Jan 21

Upcoming Scientific Meeting

27 October – 1 November 2009

42nd Annual Meeting and Scientific Exposition of the American Society of Nephrology

San Diego, CA

Contact: Website: http://www.asn-online.org/education_and_meetings/renal_week/

Email: email@asn-online.org

Tel: 202-659-0599

Disclosure: Drs. Wong and Chandraker have no disclosures to announce in association with the contents of this issue.

This activity is supported by an educational donation provided by

Amgen

©2009 Nephrology Division, Brigham and Women’s Hospital, Boston, Massachusetts, which is solely responsible for the contents. The opinions expressed in this publication do not necessarily reflect those of the publisher or sponsor, but rather are those of the author based on the available scientific literature. Publisher: **SNELL Medical Communication Inc.** in cooperation with the Nephrology Division, Brigham and Women’s Hospital. ©Nephrology Rounds is a registered trademark of **SNELL Medical Communication Inc.** All rights reserved. The administration of any therapies discussed or referred to in *Nephrology Rounds* should always be consistent with the recognized prescribing information as required by the FDA. **SNELL Medical Communication Inc.** is committed to the development of superior Continuing Medical Education.