1. Histological evolution of BK virus associated nephropathy: Importance of integrating clinical and pathological findings.

Am J Transplant. 2017 Apr 19. doi: 10.1111/ajt.14314. [Epub ahead of print]

Drachenberg CB, Papadimitriou JC, Chaudhry MR, Ugarte R, Mavanur M, Thomas B, Cangro C, Costa N, Ramos E, Weir MR, Haririan A.

ABSTRACT

Long term clinicopathological studies of BK-associated nephropathy (PyVAN) are not available. We studied 206 biopsies (71 patients), followed 3.09±1.46y after immunosuppression reduction. The biopsy features (% SV40+staining and inflammation +/- acute rejection) were correlated with viral load dynamics and serum creatinine to define the clinicopathological status (PyVCPS).

Incidence of acute rejection was 28% in the 2nd biopsy and 50% subsequently (25% mixed TCMR+AMR; rejection overall affected 38% of patients (>50% AMR). Graft loss was 15.4% (0.8-5.3y after PyVAN); 76% had complete viral clearance (mean 28weeks). The only predictors of graft loss were acute rejection (TCMR p=0.008, any type p=0.07), and increased “t” and “ci” in the 2ndbiopsy (p=0.006 and 0.048). Higher peak viremia correlated with poorer viral clearance (p=.002).

Presumptive and proven PyVAN had similar presentation, evolution and outcome. Late PyVAN (>2 years,9.8%) justifies BK viremia evaluation at any point with graft dysfunction and/or biopsy evaluation.

This study describes the histological evolution of PyVAN and corresponding clinicopathological correlations. Although the pathological features overall reflect the viral and immunological interactions, the PyVAN course remains difficult to predict based on any single feature. Appropriate clinical management requires repeat biopsies and determination of the PyVCPS at relevant time points, for corresponding personalized immunosuppression adjustment.

2. Correlation of BK Virus Neutralizing Serostatus With the Incidence of BK Viremia in Kidney Transplant Recipients.

Transplantation 2016;00: 00–00

Abend J.R., Changala M., Sathe A., Casey F., Kistler A., Chandran S., Howard A. and D. Wojciechowski.

ABSTRACT

Background. BK virus (BKV)-associated nephropathy is the second leading cause of graft loss in kidney transplant recipients.

Due to the high prevalence of persistent infection with BKV in the general population, it is possible that either the transplant recipient or donor may act as the source of virus resulting in viruria and viremia. Although several studies suggest a correlation between donor-recipient serostatus and the development of BK viremia, specific risk factors for BKV-related complications in the transplant setting remain to be established.

Methods. We retrospectively determined the pretransplant BKV neutralizing serostatus of 116 donors (D)-recipient (R) pairs using infectious BKV neutralization assays with representatives from the 4 major viral serotypes.

The neutralizing serostatus of donors and recipients was then correlated with the incidence of BK viremia during the first year posttransplantation.

Results. There were no significant differences in baseline demographics or transplant data among the 4 neutralizing serostatus groups, with the exception of calculated panel-reactive antibody which was lowest in the D+/R− group. Recipients of kidneys from donors with significant serum neutralizing activity (D+) had elevated risk for

BK viremia, regardless of recipient serostatus (D+ versus D−: odd ratio, 5.0; 95% confidence interval, 1.9-12.7]; P = 0.0008).

Furthermore, donor-recipient pairs with D+/R− neutralizing serostatus had the greatest risk for BK viremia (odds ratio, 4.9; 95% confidence interval, 1.7-14.6; P = 0.004).

Conclusions. Donor neutralizing serostatus correlates significantly with incidence of posttransplant BK viremia. Determination of donor-recipient neutralizing serostatus may be useful in assessing the risk of BKV infection in kidney transplant recipients.

3. Preemptive reduction of immunosuppression upon high urinary polyomavirus loads improves patient survival without affecting kidney graft function.

Transpl Infect Dis. 2016 Dec;18(6):872-880. doi: 10.1111/tid.12603. Epub 2016 Oct 20.

Broeders EN, Hamade A, El Mountahi F, Racapé J, Hougardy JM, Le Moine A, Vereerstraeten P.

ABSTRACT

Background: Polyomavirus (PV) is a major cause of kidney graft disease. Monitoring by polymerase chain reaction (PCR) on blood is currently recommended. In order to avoid irreversible lesions, we investigated the clinical impact of preemptive reduction of immunosuppression (IS) in kidney transplant recipients (KTR) upon detection of high urinary PV (Upv) load, including BK virus and JC virus.

Material and methods: From 2000 to 2011, in our single center, 789 consecutive KTR were distributed into 4 groups, according to the maximal Upv levels (by PCR) during the first year and the therapeutic option: (A) Upv <104 copies (cp)/mL (*n*=573), (B) ≥104 Upv <107 cp/mL (*n*=100), and (C) Upv ≥107 cp/mL (*n*=116); in group C, the IS drug doses were reduced in subgroup Ca (*n*=102) only, as 14 patients (subgroup Cb) were at risk for graft rejection.

Results: The preemptive reduction of IS (group Ca) increased patient survival as compared with all other groups (*P*<.05), did not modify graft function, and increased graft survival vs group A (risk ratio: 5.7, confidence interval: 1.8–18.1, *P*=.003). Differences for risk factors are as follows (groups Ca vs A): incidence of human leukocyte antigen (HLA) immunization (>5% panel reactive antibodies): 3% vs 8% (*P*=.05), number of HLA mismatches: 2.7 vs 2.5 (*P*=.049), and incidence of acute rejection: 9.8% vs 24.2% (*P*=.005). PV-associated nephropathy occurred only in group Ca (2% of total grafts) without effect on patient or graft outcome.

Conclusion: The reduction of IS in patients with high Upv loads is beneficial for patient survival and does not affect graft survival or graft function.

4. BK Virus in Kidney Transplant: Current Concepts, Recent Advances, and Future Directions. Exp Clin Transplant. 2016 Aug;14(4):377-84. doi: 10.6002/ect.2016.0030. Epub 2016 Jun 3.
Sharma R, Tzetzo S, Patel S, Zachariah M, Sharma S, Melendy T.

ABSTRACT
BK virus nephropathy is a challenging clinical problem in kidney transplant recipients with wide range of surveillance and management practices, based on individual experience. BK virus reactivation in kidney transplant recipients can result in BK virus nephropathy and graft loss. The most effective strategy for early diagnosis and treatment of BK virus nephropathy is regular monitoring for BK virus, currently achieved by quantification of viral DNA in blood by quantitative polymerase chain reaction. Immunosuppression reduction remains the mainstay of treatment; however, viral clearance is often followed by acute rejection, likely secondary to a delay between immune reconstitution and viral clearance. Impaired cell-mediated immune response to BK virus has been shown to correlate with progression to BK virus nephropathy, while reconstitution of this response correlates with resolution of nephropathy. There is recent research to support monitoring BK virus-specific cell-mediated immune response as a predictor of disease progression and resolution. In this article, we review the current concepts and recent developments in understanding BK virus associated disease in the context of kidney transplant and outline areas for future research.

5. Clearance of BK Virus Nephropathy by Combination Antiviral Therapy With Intravenous Immunoglobulin.

Transplantation direct Volumen: 3 Número: 4 Páginas: e142 Fecha de publicación: 2017-Apr

Kable K., Davies C., O'Connell P. J. et al.

ABSTRACT

Background. Reactivation of BK polyoma virus causes a destructive virus allograft nephropathy (BKVAN) with graft loss in 46%. Treatment options are limited to reduced immunosuppression and largely ineffective antiviral agents. Some studies suggest benefit from intravenous immunoglobulin (IVIG).

Methods. We evaluated effectiveness of adjuvant IVIG to eliminate virus from blood and tissue, in a retrospective, single-center cohort study, against standard-of-care controls. Both groups underwent reduced immunosuppression; conversion of tacrolimus to cyclosporine; and mycophenolate to leflunomide, oral ciprofloxacin, and intravenous cidofovir.

Results. Biopsy-proven BKVAN occurred in 50 kidneys at 7 (median interquartile range, 3-12) months after transplantation, predominantly as histological stage B (92%), diagnosed following by dysfunction in 46%, screening viremia in 20%, and protocol biopsy in 34%. After treatment, mean viral loads fell from 1581 ± 4220 x 10^3 copies at diagnosis to 1434 ± 70 639 midtreatment, and 0.138 ± 0.331 after 3 months ($P < 0.001$). IVIG at 1.01 ± 0.18 g/kg was given to 22 (44%) patients. The IVIG group more effectively cleared viremia (hazard ratio, 3.68; 95% confidence interval, 1.56-8.68; $P = 0.003$) and BK immunohistochemistry from repeated tissue sampling (hazard ratio, 2.24; 95%confidence interval, 1.09-4.58; $P = 0.028$), and resulted in faster (11.3 ± 10.4 months vs 29.1 ± 31.8 months, $P = 0.015$) and more complete resolution of viremia (33.3% vs 77.3%, $P = 0.044$). Numerically, fewer graft losses occurred with IVIG (27.3%vs 53.6%for control, $P = 0.06$), although graft and patient survivals were not statistically different. Acute renal dysfunction requiring pulse corticosteroid was common (59.1%vs 78.6%, $P = 0.09$), respectively, after immunosuppression reduction.

Conclusions. Combination treatment incorporating adjuvant IVIG was more effective eliminating virus from BKVAN, compared with conventional therapy. Validation by multicenter randomized trial is needed.

6. Transient versus persistent BK viremia and long-term outcomes after kidney and kidney-pancreas transplantation.

Clin J Am Soc Nephrol. 2014 Mar;9(3):553-61

Elfadawy N, Flechner SM, Schold JD et al

ABSTRACT

Background and objectives: The objective was to study the long-term impact of transient versus persistent BK viremia on kidney transplant outcomes.

Design, setting, participants, & measurements: In total, 609 recipients who underwent kidney transplant from 2007 to 2011 were screened at months 1-12 for the occurrence of polyomavirus BK viremia; 130 patients (21.7%) developed BK viremia during the first year post-transplant. BK viremia patients were classified according to duration of infection (more or less than 3 months), and BK viral loads (more or less than 10,000 copies/ml) were classified as transient low viremia (n=42), transient high viremia (n=18), persistent low viremia (n=23), and persistent high viremia (n=47). All patients were followed a median of 36 (3-66) months. The rates of BK polyomavirus-associated nephropathy, acute rejection, and 1-year graft function were compared with the polyomavirus BK-negative control group.

Results: Patient and graft survival were not significantly different among the groups. Graft function (creatinine; milligrams per deciliter) at 1 year was significantly worse in the persistent high viremia (1.75±0.6) and transient high viremia (1.85±0.7) groups compared with aviremic controls (1.47±0.4; P=0.01 and P=0.01, respectively). The incidence of BK polyomavirus-associated nephropathy was limited to the persistent high viremia group (1.3%, P<0.001). The transient high viremia (50%) and persistent high viremia (34%) groups showed significantly (P=0.01) increased incidence of acute rejection versus aviremic controls (21.5%), transient low viremia (19%), or persistent low viremia (17.3%) groups.

Conclusion: Low viral load BK viremia, either transient or persistent, was not associated with long-term transplant outcomes. Persistent high viremia was associated with a greater risk for BK polyomavirus-associated nephropathy and subsequent graft dysfunction. Although transient high viremia was not associated with BK polyomavirus-associated nephropathy, it was associated with worse graft function. These data support the role of surveillance for BK viremia after transplant.

7. BK Polyomavirus: Clinical Aspects, Immune Regulation, and Emerging Therapies
CLINICAL MICROBIOLOGY REVIEWS Volumen: 30 Número: 2 Páginas: 503-528 Fecha de publicación: APR 2017
Ambalathingal G.R., Francis R. S., Smyth M.J., et al.

SUMMARY
BK polyomavirus (BKV) causes frequent infections during childhood and establishes persistent infections within renal tubular cells and the uroepithelium, with minimal clinical implications. However, reactivation of BKV in immunocompromised individuals following renal or hematopoietic stem cell transplantation may cause serious complications, including BKV-associated nephropathy (BKVAN), ureteric stenosis, or hemorrhagic cystitis. Implementation of more potent immunosuppression and increased posttransplant surveillance has resulted in a higher incidence of BKVAN. Antiviral immunity plays a crucial role in controlling BKV replication, and our increasing knowledge about host-virus interactions has led to the development of improved diagnostic tools and clinical management strategies. Currently, there are no effective antiviral agents for BKV infection, and the mainstay of managing reactivation is reduction of immunosuppression. Development of immune-based therapies to combat BKV may provide new and exciting opportunities for the successful treatment of BKV-associated complications.

8. BK virus nephropathy: histological evolution by sequential pathology.

American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons Fecha de publicación: 2017-Mar-30 (Epub 2017 Mar 30)

Nankivell, Brian J, Renthawa, Jasveen, Sharma, Raghwa N, et al.

ABSTRACT

Reactivation of BK virus in renal allografts causes a destructive chronic infection. This single-center retrospective cohort study describes the evolution of BK virus allograft nephropathy (BKVAN) from 63 kidneys (from 61 patients) using sequential histopathology (454 biopsies, averaging 7.8 ± 2.6 per kidney) followed for 60.1 mo. Uninfected protocol biopsies formulated time-matched control Banff scores (n = 975). Interstitial inflammation occurred in 73% at diagnosis, correlating with viral histopathology (r = 0.413, p = 0.008) and amplifying early injury with accelerated interstitial fibrosis and tubular atrophy (IF/TA, p = 0.017) by 3 mo. Prodromal simian virus 40 large T antigen (SV40T)–negative inflammation with viremia preceded the histological diagnosis in 23.8%. Persistent subacute injury from viral cytopathic effect was associated with acute tubular necrosis and ongoing interstitial inflammation, culminating in IF/ TA in 86.9%. Overall, cellular interstitial infiltration mitigated the intensity of subsequent tubular injury, SV40T, and tissue viral load, assessed by sequential paired histology (p < 0.001). Graft loss was predicted by high-level viremia (hazard ratio [HR] 4.996, 95% CI 2.19–11.396, p < 0.001), deceased donor (HR 3.201, 95% CI 1.149–8.915, p = 0.026), and late acute rejection (HR 3.124, 95% CI 1.037–9.413, p = 0.043). Transplant failure occurred in 38.1%, with uncontrolled infection (58.3%) and SV40T-negative chronic rejection (41.7%) causing losses. BKVAN is characterized by subacute virus-induced tubular injury, inflammation, and progressive nephron destruction. Effective antiviral therapy remains an unmet clinical need.

9. Incidence and outcome of BK polyomavirus infection in a multicenter randomized controlled trial with renal transplant patients receiving cyclosporine-, mycophenolate sodium-, or everolimus-based low-dose immunosuppressive therapy.

Transpl Infect Dis. 2017;e12687.

van Doesum W.B., Gard L., Bemelman F.J et al.

ABSTRACT

Background: It remains unclear whether overall degree of immunosuppression or specific effects of individual immunosuppressive agents are causal for increased occurrence of BK polyomavirus (BKPyV) infection in renal transplant recipients (RTR).

Methods: A prospective, multicenter, open-label randomized controlled trial in 361 de novo RTR was performed. A total of 224 RTR were randomized at 6 months into three treatment groups with dual therapy consisting of prednisolone (Pred) plus either cyclosporine (CsA), mycophenolate sodium (MPS), or everolimus (EVL). Primary outcomes were incidence of BK viruria, BK viremia, and BKPyV-associated nephropathy (BKVAN).

Results: From 6 months, incidence of BK viruria in the MPS group (43.6%) was significantly higher than in the other groups (CsA: 16.9%, EVL: 19.8%) (*P*=.003). BKVAN was diagnosed in 3 patients, all treated with MPS (7.8%, *P*=.001). Longitudinal data analysis showed a lower BKPyV load and a significantly faster clearance of BK viruria in the CsA group compared to the MPS group (*P*=.03).

Conclusions: Treatment with MPS was associated with an increased incidence of BK viruria. Dual immunosuppressive therapy with CsA and Pred was associated with the lowest rate of BKPyV replication and the fastest clearance of the virus.

10. Pretransplantation Donor-Recipient Pair Seroreactivity Against BK Polyomavirus Predicts Viremia and Nephropathy After Kidney Transplantation.

Am J Transplant. 2017 Jan;17(1):161-172

Wunderink HF, van der Meijden E, van der Blij-de Brouwer CS et al.

ABSTRACT

Kidney transplant donors are not currently implicated in predicting BK polyomavirus (BKPyV) infection in kidney transplant recipients. It has been postulated, however, that BKPyV infection originates from the kidney allograft. Because BKPyV seroreactivity correlates with BKPyV replication and thus might mirror the infectious load, we investigated whether BKPyV seroreactivity of the donor predicts viremia and BKPyV-associated nephropathy (BKPyVAN) in the recipient. In a retrospective cohort of 407 living kidney donor-recipient pairs, pretransplantation donor and recipient sera were tested for BKPyV IgG levels and correlated with the occurrence of recipient BKPyV viremia and BKPyVAN within 1 year after transplantation. Donor BKPyV IgG level was strongly associated with BKPyV viremia and BKPyVAN ($p < 0.001$), whereas recipient BKPyV seroreactivity showed a nonsignificant inverse trend. Pairing of high-BKPyV-seroreactive donors with low-seroreactive recipients resulted in a 10-fold increased risk of BKPyV viremia (hazard ratio 10.1, 95% CI 3.5-29.0, $p < 0.001$). In multivariate analysis, donor BKPyV seroreactivity was the strongest pretransplantation factor associated with viremia ($p < 0.001$) and BKPyVAN ($p = 0.007$). The proportional relationship between donor BKPyV seroreactivity and recipient infection suggests that donor BKPyV seroreactivity reflects the infectious load of the kidney allograft and calls for the use of pretransplantation BKPyV serological testing of (potential) donors and recipients.

11. High-dose steroid therapy in BK viremia adversely affected the long-term graft function after kidney transplantation

Transplant Infectious Disease Volumen: 18 Número: 6 Páginas: 844-849 Fecha de publicación: DEC 2016

Kim H., Yu H., Baek C.H. et al.

ABSTRACT

Background: Although high-dose steroid therapy has been attempted for the management of clinically suspected allograft rejection, before testing for BK viral activity or acute cellular rejection accompanied by BK polyomavirus nephropathy, its long-term outcome remains unknown. We investigated the impact of high-dose steroids on BK viral activity and long-term graft outcomes in patients with BK viremia.

Methods: The study population comprised 144 kidney transplant recipients with BK viremia. They were divided into 2 groups based on the amount of steroids administered: low-dose group (<2 g, *n*=123) or high-dose group (≥2 g, *n*=21).

Results: The baseline serum BK viral loads were 5.4±1.1 log cp/mL in the low-dose group and 6.0±1.3 in the high-dose group (*P*=.054). These changed to 5.2±1.3 and 6.1±1.4, 1 month after steroid treatment (*P*=.03) and 4.9±1.3 and 5.9±1.4 at 2 months (*P*=.033), respectively. From 3 months to 1 year, the serum BK viral titers were not different between groups. Kaplan-Meier analyses demonstrated that the rates of the decline of graft function and graft failure were higher in the high-dose group (*P*=.02 and *P*=.04, respectively). High-dose steroids (*P*=.012, hazard ratio [HR] 5.04, 95% confidence interval [CI] 1.42–17.85) and log serum BK viral load at 2 months after steroid treatment (*P*=.042, HR 1.52, 95% CI 1.02–2.28) were independent risk factors for the decline of graft function.

Conclusion: High-dose steroids induced BK viral activation and subsequently resulted in poor long-term graft function and early graft failure in patients with BK viremia.

12. Different risk factor profiles distinguish early-onset from late-onset BKV-replication.
Transpl Int. 2015 Sep;28(9):1081-91.
Schachtner T, Babel N, Reinke P.

ABSTRACT
Two of three reactivations of latent BKV-infection occur within the first 6 months after renal transplantation. However, a clear differentiation between early-onset and late-onset BKV-replication is lacking. Here, we studied all kidney transplant recipients (KTRs) at our single transplant center between 2004 and 2012. A total of 103 of 862 KTRs were diagnosed with BK viremia (11.9%), among which 24 KTRs (2.8%) showed progression to BKV-associated nephropathy (BKVN). Sixty-seven KTRs with early-onset BKV-replication (65%) and 36 KTRs with late-onset BKV-replication (35%) were identified. A control group of 598 KTRs without BKV-replication was used for comparison. Lymphocyte-depleting induction, CMV-reactivation, and acute rejection increased the risk of early-onset BKV-replication ($P < 0.05$). Presensitized KTRs undergoing renal retransplantation were those at increased risk of late-onset BKV-replication ($P < 0.05$). Among KTRs with BK viremia, higher doses of mycophenolate increased the risk of progression to BKVN ($P = 0.004$). KTRs with progression to BKVN showed inferior allograft function ($P < 0.05$). KTRs with late-onset BK viremia were more likely not to recover to baseline creatinine after BKV-replication ($P = 0.018$). Our data suggest different risk factors in the pathogenesis of early-onset and late-onset BKV-reactivation. While a more intensified immunosuppression is associated with early-onset BKV-replication, a chronic inflammatory state in presensitized KTRs may contribute to late-onset BKV-replication.

13. BK Polyomavirus and the Transplanted Kidney: Immunopathology and Therapeutic Approaches

Transplantation 2016;100: 2276–2287

Lamarche C., Orio J., Collette S. et al.

ABSTRACT

BK polyomavirus is ubiquitous, with a seropositivity rate of over 75% in the adult population. Primary infection is thought to occur in the respiratory tract, but asymptomatic BK virus latency is established in the urothelium. In immunocompromised host, the virus can reactivate but rarely compromises kidney function except in renal grafts, where it causes a tubulointerstitial inflammatory response similar to acute rejection. Restoring host immunity against the virus is the cornerstone of treatment. This review covers the virus-intrinsic features, the posttransplant microenvironment as well as the host immune factors that underlie the pathophysiology of polyomavirus-associated nephropathy. Current and promising therapeutic approaches to treat or prevent this complication are discussed in relation to the complex immunopathology of this condition.

14. Influence of tacrolimus metabolism rate on BKV infection after kidney transplantation

Scientific Reports, 6: 32273 Fecha de publicación: AUG 30 2016

Thoelking G., Schmidt C., Koch R. et al.

ABSTRACT

Immunosuppression is the major risk factor for BK virus nephropathy (BKVN) after renal transplantation (RTx). As the individual tacrolimus (Tac) metabolism rate correlates with Tac side effects, we hypothesized that Tac metabolism might also influence the BKV infection risk. In this case-control study RTx patients with BK viremia within 4 years after RTx (BKV group) were compared with a BKV negative control group. The Tac metabolism rate expressed as the blood concentration normalized by the daily dose (C/D ratio) was applied to assess the Tac metabolism rate. BK viremia was detected in 86 patients after a median time of 6 (0–36) months after RTx. BKV positive patients showed lower Tac C/D ratios at 1, 3 and 6 months after RTx and were classified as fast Tac metabolizers. 8 of 86 patients with BK viremia had histologically proven BKN and a higher median maximum viral load than BKV patients without BKN (441,000 vs. 18,572 copies/mL). We conclude from our data that fast Tac metabolism (C/D ratio <1.05) is associated with BK viremia after RTx. Calculation of the Tac C/D ratio early after RTx, may assist transplant clinicians to identify patients at risk and to choose the optimal immunosuppressive regimen.

15. BK virus nephropathy in renal transplant recipients

Nephrology Volumen: 21 Número: 8 Páginas: 647-654 Fecha de publicación: AUG 2016

Jamboti J.S.

ABSTRACT

BK virus nephropathy (BKVN) occurs in up to 10% of renal transplant recipients and can result in graft loss. The reactivation of BK virus in renal transplant recipients is largely asymptomatic, and routine surveillance especially in the first 12–24months after transplant is necessary for early recognition and intervention. Reduced immunosuppression and anti-viral treatment in the early stages may be effective in stopping BK virus replication. Urinary decoy cells, although highly specific, lack sensitivity to diagnose BKVN. Transplant biopsy remains the gold standard to diagnose BKVN, good surrogate markers for surveillance using quantitative urinary decoy cells, urinary SV40 T immunochemical staining or polyoma virus-Haufen bodies are offered by recent studies. Advanced BKVN results in severe tubulo-interstitial damage and graft failure. Retransplantation after BKVN is associated with good outcomes. Newer treatment modalities are emerging.

16. Strategies to prevent BK virus infection in kidney transplant recipients

Current Opinion In Infectious Diseases Volumen: 29 Número: 4 Páginas: 353-358 Fecha de publicación: AUG 2016

Wright A.J., Gill J.S.

ABSTRACT

Purpose of review: Despite improvements in posttransplant care, BK virus (BKV) remains one of the most challenging posttransplant infections in kidney transplant recipients with high rates of allograft failure. In the absence of well tolerated and efficacious viral specific therapeutics, treatment is primarily focused on reduction of immunosuppression, which poses a risk of rejection and fails to lead to viral clearance in a number of patients.

Recent findings: Recent work has turned toward preventive therapies analogous to those used for other infections like cytomegalovirus. These efforts have focused on the use of quinolone antibiotic prophylaxis to prevent BKV infection and pretransplant vaccination to boost humoral and cellular immunity.

Summary: Despite promising in-vitro and observational data, quinolone antibiotic prophylaxis has not been effective in preventing BKV infection in prospective studies. However, prophylaxis with newer less toxic viral specific agents such as brincidofovir – the lipid oral formulation of cidofovir – may yet prove effective. Strategies focused on eliciting a humoral immune response to recombinant virus-like particles or using adoptive transfer of BKV-specific T cells have also shown significant potential to prevent BKV infection in organ transplant recipients.

17. Optimal use of plasma and urine BK viral loads for screening and predicting BK nephropathy

BMC Infectious Diseases Volumen: 16 Número de artículo: 342 Fecha de publicación: JUL 22 2016

Boan P., Hewison C., Swaminathan R. et al.

ABSTRACT

Background: BK virus is a polyoma virus causing renal allograft nephropathy. Reduction of immunosuppression with the early recognition of significant BK viral loads in urine and plasma can effectively prevent BKV associated nephropathy (BKVN), however the optimal compartment and frequency of BK viral load measurement post renal transplantation are undetermined. Our purpose was to examine time to detection and viral loads in urine compared to plasma, and establish viral load cut-offs associated with histological BKVN.

Methods: We performed a retrospective analysis of the BKV screening frequency and compartment(s) of 277 adult renal transplant recipients (RTR).

Results: BKVN was histologically diagnosed in 17 (6.1 %) RTR. In cases where both urine and plasma were tested fortnightly for 6 months (n = 53), BKV was detected in the urine 29 days earlier than plasma. Fortnightly (n = 72) versus 3-monthly (n = 78) testing demonstrated that BKV was detected in the urine significantly earlier (median 63 versus 97 days, $p = 0.001$) and at a lower level (median 3.27 versus 6.71 $\log_{10}$ c/mL, $p < 0.001$) with more frequent testing, but this difference was not evident in plasma first detection (80 versus 95 days, $p = 0.536$) or first positive viral load (3.18 versus 3.30 log10 c/mL, $p = 0.603$). The optimum cut-off BK viral load for histological diagnosis of BKVN was 4. 10 $\log_{10}$ c/mL for the first positive urine, 3.79 $\log_{10}$ c/mL for the first positive plasma, 9.24 $\log_{10}$ c/mL for the peak urine, and 4.53 $\log_{10}$ c/mL for the peak plasma.

Conclusions: Frequent urinary BK viral load screening for the prevention of BKVN is suggested due to its high sensitivity and earlier detection.

18. Risk Factors for BK Polyoma Virus Treatment and Association of Treatment With Kidney Transplant Failure: Insights From a Paired Kidney Analysis

Transplantation 2016;100: 854–861

Thangaraju S., Gill J., Wright A. et al.

ABSTRACT

Background: Identification of risk factors for BK polyoma virus (BKPyV) without confounding by donor factors and era effects in paired analysis may inform strategies to prevent BKPyV.

Methods: In this analysis of 21,575 mate kidney pairs in the Scientific
Registry of Transplant Recipients between 2004 and 2010, the presence of a treatment code for BKPyV virus in follow-up forms was used to identify pairs in which 1 of 2mate kidneys was treated (discordant treatment) or both mate kidneys were treated (concordant treatment).

Results: Among 1975 discordant pairs, younger than 18 years or 60 years or older,male sex, HLA mismatch or 4 greater, acute rejection, and depleting antibody induction had a higher odds of treatment, whereas diabetes and sirolimus had a lower odds of treatment, and treatment was associated with a higher risk of allograft failure (hazards ratio, 2.01; 95% confidence interval, 1.63-2.48). The rate of concordant treatment (0.81%) was 2.8 times higher than expected. Concordant treatment was associated with nonwhite donor ethnicity, donation after circulatory death, transplantation after 2008, and transplantation of mate kidneys in the same center.

Conclusions: This analysis of kidneys from the same donor in which only 1 transplant was treated for BKPyV identifies specific risk factors (age <18 or ≥ 60 years, male sex, depleting antibody, HLA mismatch ≥ 4) for BKPyV and provides an estimate of the BKPyV-associated risk of allograft failure (hazards ratio = 2.01) without confounding by donor factors or era effects. The higher than expected rate of concordant treatment suggests the importance of donor factors in BKPyV pathogenesis and warrants further study.

19. Sustained BK viruria as an early marker for the development of BKV-associated nephropathy: analysis of 4128 urine and serum samples

Transplantation. 2009 Jul 15;88(1):89-95.

Babel N, Fendt J, Karaivanov S, Bold G. et al.

ABSTRACT

Background: BKV reactivation plays the causative role in the development of BKV-associated nephropathy (BKVAN). Because of the lack of effective therapy, early diagnosis of BKV reactivation is paramount for the prevention of BKVAN. Resting in uroepithelial cells, BKV is excreted first in urine before it can be detected in plasma. The present study analyzed predictive value of BK viruria for the development of BK viremia and its possible advantage for the early BKVAN prediction.

Methods: Total of 4128 urine and serum samples obtained from renal transplant patients were analyzed for BKV positivity by real-time polymerase chain reaction in 433 patients in cross-sectional and in 233 patients in longitudinal manner, respectively. The prospective longitudinal analysis included seven measurements during the first posttransplant year.

Results: A total of 7% and 19% patients were positive for BKV in serum and urine, respectively. Sustained BK viruria showed sensitivity of 100% and specificity of 94% for BK viremia and was associated with significantly higher level of BK load than the patients with transient viruria ($P<0.01$). Interestingly, BK viremia was preceded by BK viruria: the peak of viral load and number of positive patients appeared during the third and fifth posttransplant month for urine and serum, respectively. BKVAN diagnosed in 21.4% of patient with persistent BK viruria appeared 5 and 11 weeks after BKV reactivation in serum and urine, respectively, was detected.

Conclusion: Sustained BK viruria is a reliable marker allowing an early identification of patients at high risk of BKVAN development and therefore assure precocious therapeutic interventions.

20. Fluoroquinolone prophylaxis in preventing BK polyomavirus infection after renal transplant: A systematic review and meta-analysis

Kaohsiung Journal of Medical Sciences (2016) 32, 152-159

Song T-R; Rao Z-S, Qiu Y. et al.

ABSTRACT

Previous studies regarding the prevention of BK viremia following renal transplantation with fluoroquinolone have yielded conflicting results. The purpose of this systematic review was to examine the evidence regarding the efficacy of fluoroquinolone in preventing BK polyomavirus infection following renal transplantation. We searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials for research articles published prior to January 2015 using keywords such as “fluoroquinolone,” “BK viremia,” and “renal transplantation.” We extracted all types of study published in English. The primary outcome was BK viremia and viruria at 1 year post-transplantation. Secondary outcomes were BK virus-associated nephropathy (BKVN), graft failure, and fluoroquinolone-resistant infection. We identified eight trials, including a total of 1477 participants with a mean duration of fluoroquinolone prophylaxis of >1 month. At 1 year, fluoroquinolone prophylaxis was not associated with a decreased incidence of BK viremia [risk ratio (RR), 0.84; 95% confidence interval (95% CI), 0.58-1.20). No significant differences in BKVN (RR, 0.88; 95% CI, 0.37-2.11), risk of graft failure due to BKVN (RR, 0.68; 95% CI, 0.29-1.59), or fluoroquinolone-resistant infection (RR, 1.08; 95% CI, 0.64-1.83) were observed between the fluoroquinolone prophylaxis and control groups. The results of this study suggest that fluoroquinolone is ineffective in preventing BK polyomavirus infection following renal transplantation.

21. Pilot conversion trial from mycophenolic acid to everolimus in ABO-incompatible kidney-transplant recipients with BK viruria and/or viremia

Transplant International Volumen: 29 Número: 3 Páginas: 315-322 Fecha de publicación: MAR 2016

Belliere J., Kamar N., Mengelle C. et al.

SUMMARY

Immunosuppression using everolimus (EVR) plus low-dose tacrolimus (Tac) is commonly used in organ transplantation. EVR has potential antiviral effects. Herein, the long-term outcomes and impacts of Tac-EVR on the BK virus are reported in ABO-incompatible kidney-transplant recipients. The initial immunosuppressive regimen combined steroids, Tac, and mycophenolic acid (MPA). At a median of 141 (34–529) days post-transplantation, seven stable ABO-incompatible kidney-transplant recipients were converted from MPA to EVR because of active BK replication, and compared with a reference group of fourteen ABO-incompatible patients receiving classical Tac plus MPA. At 1 month before conversion, at 1, 3 months after, and at last follow-up, clinical and biological parameters were monitored. The median time from conversion to the last follow-up was 784 (398-866) days. Conversion to EVR caused no change to rejection episodes or immunological status (isoagglutinin titers, anti-HLA antibodies). At last follow-up, median eGFR was similar in the Tac-MPA versus Tac-EVR group (40 [range: 14–56] vs. 54.5 ml/min/1.73 m^2 [range: 0–128], P = 0.07). The major adverse event was dyslipidemia. Interestingly, conversion from MPA to EVR decreased BK viral load in five patients. ABO-incompatible kidney-transplant recipients with an active BK virus infection may benefit from conversion to EVR.

22. BK Polyomavirus Replication in Renal Tubular Epithelial Cells Is Inhibited by Sirolimus, but Activated by Tacrolimus Through a Pathway Involving FKBP-12.

Am J Transplant. 2016 Mar;16(3):821-32.

Hirsch HH, Yakhontova K, Lu M, Manzetti J.

ABSTRACT

BK polyomavirus (BKPyV) replication causes nephropathy and premature kidney transplant failure. Insufficient BKPyV-specific T cell control is regarded as a key mechanism, but direct effects of immunosuppressive drugs on BKPyV replication might play an additional role. We compared the effects of mammalian target of rapamycin (mTOR)- and calcineurin-inhibitors on BKPyV replication in primary human renal tubular epithelial cells. Sirolimus impaired BKPyV replication with a 90% inhibitory concentration of 4 ng/mL by interfering with mTOR-SP6-kinase activation. Sirolimus inhibition was rapid and effective up to 24 h postinfection during viral early gene expression, but not thereafter, during viral late gene expression. The mTORC-1 kinase inhibitor torin-1 showed a similar inhibition profile, supporting the notion that early steps of BKPyV replication depend on mTOR activity. Cyclosporine A also inhibited BKPyV replication, while tacrolimus activated BKPyV replication and reversed sirolimus inhibition. FK binding protein 12kda (FKBP-12) siRNA knockdown abrogated sirolimus inhibition and increased BKPyV replication similar to adding tacrolimus. Thus, sirolimus and tacrolimus exert opposite effects on BKPyV replication in renal tubular epithelial cells by a mechanism involving FKBP-12 as common target. Immunosuppressive drugs may therefore contribute directly to the risk of BKPyV replication and nephropathy besides suppressing T cell functions. The data provide rationales for clinical trials aiming at reducing the risk of BKPyV replication and disease in kidney transplantation.

23. Place of mTOR inhibitors in management of BKV infection after kidney transplantation.

J Nephropathol. 2016; 5(1): 1-7

Jouve T., Rostaing L. and Malvezzi p.

ABSTRACT

Context: BK virus (BKV) viremia and BKV-associated nephropathy (BKVAN) have become a serious nuisance to kidney transplant (KT) patients since the mid-nineties, when the incidence of this disease has increased significantly.

Evidence Acquisition: Directory of open access journals (DOAJ), EMBASE, Google Scholar, PubMed, EBSCO, and Web of Science have been searched.

Results: Many hypothesis have been made as to why this phenomenon has developed; it is of general opinion that a more potent immunosuppression is at the core of the problem. The use of the association of tacrolimus (TAC) with mycophenolic acid (MPA) has gained momentum in the same years as the increase in BKV viremia incidence making it seem to be the most likely culprit. m-TOR inhibitors (m-TORIs) have been shown to have antiviral properties in vitro and this fact has encouraged different transplant teams to use these agents when confronted with BKV infection (viremia or nephropathy). However, the results are mitigated. There had been conflicting results for example when converting from TAC-to sirolimus-based immunosuppression in the setting of established BKVAN.

Conclusions: In order to prevent BKV infection we have to minimize to some extent immunosuppression, but it is not always possible, e.g. in high immunological risk patients. Conversely, we could use m-TORIs associated with low-dose calcineurin inhibitors (CNIs). This could be actually the key to a safe immunosuppression regimen both from the immunological stand point and from the viral one.

24. Evaluation of leflunomide for the treatment of BK viremia and biopsy proven BK nephropathy; a single center experience.

J Nephropathol. 2016;5(1):34-37

Nesselhauf N., Strutt J. and Bastani B.

ABSTRACT

Background: BK virus reactivation is a significant complication following renal transplantation that can result in graft failure. Reduction of immunosuppression and substitution of leflunomide for mycophenolate mofetil (MMF) has been used to treat this entity.

Objectives: To evaluate the use of leflunomide in BK viremia (BKV) and biopsy proven BK nephropathy (BKN) in kidney and kidney-pancreas transplant recipients.

Patients and Methods: We retrospectively reviewed 28 kidney and kidney-pancreas transplant recipients who had received leflunomide for BKV from January 2006 to November 2012. Demographics, time to BKV diagnosis, biopsy findings, rejection episodes, and laboratory data were recorded.

Results: The average (mean ± SD) time to BKV from time of transplant was 316.1 ± 368.0 days (62-1708 days). At time of diagnosis, 64% of patients had their maintenance immunosuppression reduced. The indications for leflunomide administration were; BKV and biopsy proven acute rejection (BPAR) (50%), biopsy proven BKN (18%), or persistent BKV (25%). Therapeutic levels (50-100 mcg/mL) were achieved in only 54% of patients, and 60% of them had required a leflunomide dose of at least 60 mg/day. BK virus was cleared from the serum on average of 151 ± 145.2 days (17-476 days). At study commencement, 29% of patients had remained on leflunomide due to persistent BKV.

Conclusions: In our study, most patients required at least a 60 mg daily dose of leflunomide to achieve therapeutic levels and to clear the virus compared to the standard 40 mg daily dose. Delaying therapy may result in progressive BKV and BKN.

25. High-level viruria as a screening tool for BK virus nephropathy in renal transplant recipients.
Kidney Res Clin Pract. 2016 Sep;35(3):176-81.
Chon WJ, Aggarwal N, Kocherginsky M et al.

ABSTRACT
Background: Although early monitoring of BK virus infection in renal transplant patients has led to improved outcomes over the past decade, it remains unclear whether monitoring for viremia is the best screening tool for BK virus nephropathy (BKVN).
Methods: We conducted a retrospective review of the medical records of 368 renal transplant recipients who had a minimum of 18 months of posttransplantation follow-up. The relationship between the presence of BK viruria and a composite end point of BK viremia/BKVN was established, and the predictive value of high-grade BK viruria for development of viremia/BKVN was determined.
Results: High grade of BK viruria was present in 110 (30.1%) of the renal transplant recipients. BK viremia/BKVN was present in 64 (17.4%) patients and was 50 times more likely to be present in patients with high-grade BK viruria. The risk of developing BK viremia/BKVN was 3 times higher in high-grade viruria patients, and viruria preceded viremia by nearly 7 weeks.
Conclusion: The presence of high-grade viruria is an early marker for developing BK viremia/BKVN. Detection of high-grade viruria should prompt early allograft biopsy and/or preemptive reduction in immunosuppression.

26. Increased Frequency of BK Virus-Specific Polyfunctional CD8+ T Cells Predict Successful Control of BK Viremia After Kidney Transplantation.

Transplantation. 2017 Jun;101(6):1479-1487.

Schaenman JM, Korin Y, Sidwell T, et al.

ABSTRACT

Background: BK virus infection remains an important cause of loss of allograft function after kidney transplantation. We sought to determine whether polyfunctional T cells secreting multiple cytokines simultaneously, which have been shown to be associated with viral control, could be detected early after start of BK viremia, which would provide insight into the mechanism of successful antiviral control.

Methods: Peripheral blood mononuclear cells collected during episodes of BK viral replication were evaluated by multiparameter flow cytometry after stimulation by overlapping peptide pools of BK virus antigen to determine frequency of CD8+ and CD4+ T cells expressing 1 or more cytokines simultaneously, as well as markers of T-cell activation, exhaustion, and maturation.

Results: BK virus controllers, defined as those with episodes of BK viremia of 3 months or less, had an 11-fold increase in frequency of CD8+ polyfunctional T cells expressing multiple cytokines, as compared with patients with prolonged episodes of BK viremia. Patients with only low level BK viremia expressed low frequencies of polyfunctional T cells. Polyfunctional T cells were predominantly of the effector memory maturation subtype and expressed the cytotoxicity marker CD107a.

Conclusions: Noninvasive techniques for immune assessment of peripheral blood can provide insight into the mechanism of control of BK virus replication and may allow for future patient risk stratification and customization of immune suppression at the onset of BK viremia.

27. Kidney retransplantation for BK virus nephropathy with active viremia without allograft nephrectomy

J Nephrol (2015) 28:773–777

Huang J., Danovitch G., Phuong-Thu P. et al.

ABSTRACT

BK virus nephropathy is an important cause of kidney allograft failure. Retransplantation has been successfully performed for patients with previous allograft loss due to BK virus nephropathy; however, whether allograft nephrectomy and viral clearance are required prior to retransplantation is controversial. Some recent studies have suggested that retransplantion can be successfully achieved without allograft nephrectomy if viremia is cleared prior to retransplant. The only published experience of successful retransplantation in the presence of active viremia occurred in the presence of concomitant allograft nephrectomy of the failing kidney. In this report, we describe a case of successful repeat kidney transplant in a patient with high-grade BK viremia and fulminant hepatic failure without concomitant allograft nephrectomy performed under the setting of a simultaneous liver-kidney transplant.

28. Increased Frequency of BK Virus-Specific Polyfunctional CD8+ T Cells Predict Successful Control of BK Viremia After Kidney Transplantation.
Transplantation. 2017 Jun;101(6):1479-1487
Schaenman JM, Korin Y, Sidwell T et al.

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Methods: Peripheral blood mononuclear cells collected during episodes of BK viral replication were evaluated by multiparameter flow cytometry after stimulation by overlapping peptide pools of BK virus antigen to determine frequency of CD8+ and CD4+ T cells expressing 1 or more cytokines simultaneously, as well as markers of T-cell activation, exhaustion, and maturation.
Results: BK virus controllers, defined as those with episodes of BK viremia of 3 months or less, had an 11-fold increase in frequency of CD8+ polyfunctional T cells expressing multiple cytokines, as compared with patients with prolonged episodes of BK viremia. Patients with only low level BK viremia expressed low frequencies of polyfunctional T cells. Polyfunctional T cells were predominantly of the effector memory maturation subtype and expressed the cytotoxicity marker CD107a.
Conclusions: Noninvasive techniques for immune assessment of peripheral blood can provide insight into the mechanism of control of BK virus replication and may allow for future patient risk stratification and customization of immune suppression at the onset of BK viremia.

29. Clinical Utility of Urinary Cytology to Detect BK Viral Nephropathy

Transplantation 2015;99: 1715–1722

Nankivell B. J., Renthawa J., Jeoffreys N. et al.

ABSTRACT

Background. Reactivation of BK polyoma virus can result in destructive viral allograft nephropathy (BKVAN) with limited treatment options. Screening programs using surrogate markers of viral replication are important preventive strategies, guiding immunosuppression reduction.

Methods. We prospectively evaluated the diagnostic test performance of urinary decoy cells and urinary SV40T immunochemistry of exfoliated cells, to screen for BKVAN, (defined by reference histology with SV40 immunohistochemistry, n = 704 samples), compared with quantitative viremia, from 211 kidney and 141 kidney-pancreas transplant recipients.

Results. The disease prevalence of BKVAN was 2.6%. Decoy cells occurred in 95 of 704 (13.5%) samples, with a sensitivity of 66.7%, specificity of 88.6%, positive predictive value (PPV) of 11.7%, and negative predictive value of 98.5% to predict histologically proven BKVAN. Quantification of decoy cells improved the PPV to 32.1% (10 ≥ cells threshold). Immunohistochemical staining of urinary exfoliated cells for SV40T improved sensitivity to 85.7%, detecting atypical or degenerate infected cells (specificity of 92.3% and PPV of 33.3%), but was hampered by technical failures. Viremia occurred in 90 of 704 (12.8%) with sensitivity of 96.3%, specificity of 90.3%, PPV of 31.5%, and negative predictive value of 99.8%. The receiver-operator curve performance of quantitative viremia surpassed decoy cells (area under the curve of 0.95 and 0.79, respectively, P = 0.0018 for differences). Combining decoy cell and BK viremia in a diagnostic matrix improved prediction of BKVAN and diagnostic risk stratification, especially for high-level positive results.

Conclusions. Although quantified decoy cells are acceptable surrogate markers of BK viral replication with unexceptional test performances, quantitative viremia displayed superior test characteristics and is suggested as the screening test of choice.

30. Persistent BK Viremia Does Not Increase Intermediate-Term Graft Loss but Is Associated with De Novo Donor-Specific Antibodies

J Am Soc Nephrol 26: 966–975, 2015

Sawinski D., Forde K.A., Trofe-Clark J. et al.

ABSTRACT

There are limited data regarding intermediate-term outcomes in patients with persistent BK viremia. Other viral infections have been implicated in the development of allosensitization through heterologous immunity, but the relationship between BK viremia and donor-specific antibodies (DSAs) is unexplored. In 2008, we initiated routine post-transplant BK viremia and DSA screening at our center; 785 kidney or kidney–pancreas transplant recipients were included in our study. Of these recipients, 132 (17%) recipients developed BK viremia during the study period. The median duration of BK viremia was 140 days (interquartile range=40–393 days), and persistent BK viremia was defined as lasting ≥140 days. Kaplan–Meier curves were generated to assess differences in patient and allograft survival on the basis of BK viremia status; survival was modeled using Cox proportional hazard regression. After a median follow-up of 3 years, there was no significant difference in terms of patient (hazard ratio [HR], 0.83; 95% confidence interval [95% CI], 0.28 to 2.49) or allograft survival (HR, 0.80; 95% CI, 0.37 to 1.73) between patients with and without BK viremia, which was confirmed in a time-varying analysis. In our logistic regression model, persistent BK viremia was strongly associated with the development of class II (HR, 2.55; 95% CI, 1.30 to 4.98) but not class I (HR, 1.13; 95% CI, 0.46 to 2.77) DSAs. These data suggest that persistent BK viremia does not negatively affect intermediate-term patient or allograft survival but is associated with increased risk for *de novo* DSA, although the exact mechanism is unclear.

31. BK virus infection following kidney transplantation: an overview of risk factors, screening strategies, and therapeutic interventions.

Curr Opin Organ Transplant. 2014 Aug;19(4):401-12

Pham PT, Schaenman J, Pham PC.

ABSTRACT

Purpose of review:

In recipients of kidney transplants, the emergence of BK virus (BKV)-associated clinical syndromes, such as viruria, viremia, and BK nephropathy, coincided with the advent of potent immunosuppressive therapy. There is currently no standardized protocol for the management of BK viruria or viremia, or established BK nephropathy. Suggested risk factors for BKV replication and a literature overview on various treatment strategies for BKV-associated clinical syndromes are presented, followed by the authors' proposed approach for screening, monitoring, and treatment of post-transplant BKV infection.

RECENT FINDINGS:

BKV infection can occur under all combinations of immunosuppressive therapy. Although both humoral and cellular immunity may be essential, BKV-specific T-cell immunity appears to play a pivotal role in controlling BKV replication. Monitoring BKV-specific immune response might prove useful in guiding therapeutic intervention. The beneficial effects of antiviral agents remain unclear. Development of T-cell or antibody-based vaccines against BKV is a subject of future research.

SUMMARY:

In the absence of conclusive evidence that any particular immunosuppressive agent has a specific influence over another on BKV infection risk and the unclear benefit of antiviral agents, intensive monitoring of serum BKV using PCR and immunological containment of BKV replication should remain the mainstay of therapy. The routine recommendations of antiviral agents in the treatment of BKV-associated clinical syndromes await results of large prospective randomized trials.

32. Polyomaviruses and disease: is there more to know than viremia and viruria?
Curr Opin Organ Transplant. 2015 Jun;20(3):348-58
Nickeleit V, Singh HK.

ABSTRACT
Purpose of review: Polyomavirus nephropathy (PVN) mainly caused by BK virus (BKV) remains the most common productive viral infection of the kidney. Over the past decade, clinical interest often focused on BK viremia and viruria as the diagnostic mainstays of patient management. The purpose of this review is to discuss viral nephropathy in the context of BK viremia and viruria and new strategies to optimize diagnostic accuracy and patient management. The emerging roles of polyomaviruses in oncogenesis, salivary gland disease, and post-bone marrow transplantation as well as novel Polyomavirus strains are highlighted.
Recent findings: Areas of investigation include proposals by the Banff working group on the classification of PVN and studies on PVN progression and resolution, including the role cellular immune responses may play during reconstitution injury. New noninvasive strategies to optimize the diagnosis of PVN, that is, the urinary 'polyomavirus-haufen' test and mRNA expression levels for BKV in the urine, hold great promise to accurately identify patients with viral nephropathy. Tools are now available to separate 'presumptive' from 'definitive' disease in various patient cohorts including individuals post-bone marrow transplantation. Recent observations also point to a currently underrecognized role of polyomaviruses in oncogenesis post-transplantation and salivary gland disease in patients with HIV-AIDS.
Summary: This review summarizes recent studies on PVN and the significance of the BKV strain in disease. Current paradigms for patient management post-(renal) transplantation are discussed in the setting of new observations. Issues that still require clarification and further validation are highlighted.

33. Conversion to a sirolimus-based regimen is associated with lower incidence of BK viremia in low-risk kidney transplant recipients

Transpl Infect Dis 2015: 17: 66–72

Tohme, F. A.; Kalil, R. S.; Thomas, C. P.

ABSTRACT

Background: BK viral nephropathy is an increasingly recognized cause of early allograft loss in kidney transplantation. This study aimed to determine whether a sirolimus (Sir)-based calcineurin inhibitor-sparing regimen is associated with a lower incidence of BK viremia.

Methods: This was a single-center retrospective study. Patients were either on tacrolimus (Tac)-based or on Sir-based immunosuppression. Conversion from Tac to Sir occurred at or after 3 months if patients were<62 years of age, had calculated panel reactive antibodies of<20%, and did not have acute early rejection.

Results: Incidence of clinically significant BK viremia was 17.9% in the Tac group and 4.3% in the Sir group. Cox regression multivariate analysis showed that male gender (hazard ratio [HR] = 2.87) and switch to Sir (HR = 0.333) impacted the incidence of BK viremia. Kaplan–Meier analysis showed a higher BK-free survival in the Sir group. A trend was seen toward shorter time to resolution of BK viremia and lower peak viremia in the Sir group. Patients on Sir had a higher estimated glomerular filtration rate at each time point; 34% of patients discontinued Sir because of side effects.

Conclusion: Conversion to Sir-based maintenance immunosuppression at or about 3 months after kidney transplantation correlates with a lower incidence of BK viremia.

34. Screening Algorithm for BK Virus-Associated Nephropathy Using Sequential Testing of Urinary Cytology: A Probabilistic Model Analysis

Am J Nephrol 2015;42:410–417

Ma M. K. M., Leung A. Y. H., Lo K. Y. et al.

ABSTRACT

Background: Incorporating urinary cytology in BK virus (BKV) screening algorithm potentially reduces the screening cost for BK viral nephropathy. We aimed to evaluate the test performances and screening cost of sequential 2-stage screening consisting of urine cytology followed by BKV serum quantitative polymerase chain reaction (PCR).

Methods: Ninety-five kidney transplant recipients who had BKV serum quantitative PCR/urine cytology tested and verified with histopathology (the reference gold standard) were included. A probabilistic model was constructed to evaluate the test performance and screening cost of 2-stage screening, and was compared with screening with urine cytology or serum viral load alone.

Results: At a viral load threshold of ≥ 10 4 copies/ ml, the sensitivity and specificity of quantitative PCR alone were 83% (95% CI 69–96) and 91% (95% CI 83–97), respectively. The sensitivity and specificity of urine cytology alone were 91% (95% CI 79–100) and 74% (95% CI 60–91), respectively.

Sequential 2-stage screening resulted in loss in sensitivity but a net gain in specificity (viral load threshold ≥ 10 4 copies/ml – sensitivity, 75% (95% CI 60–91); specificity, 98% (95% CI 95–99)). Two-stage screening also had superior positive predictive value and is cost effective when BKV-associated nephropathy prevalence is below 94%.

Conclusions: Our study had demonstrated a favorable test performance and cost efficiency of 2-stage BKV screening.

35. 45 years after the discovery of human polyomaviruses BK and JC: Time to speed up the understanding of associated diseases and treatment approaches.
Crit Rev Microbiol. 2017 Mar;43(2):178-195.
Barth H., Solis M., Lepiller Q. et al.

ABSTRACT
Nearly 45 years after the discovery of the first two human polyomaviruses BK and JC, their life-long persistence and mechanisms of pathogenesis remain poorly understood and efficient antiviral treatments are severely lacking. In this review, we sought to provide an update on recent advances in understanding the life cycle of these two viruses, particularly focusing on their interaction with the host immune system and pathogenesis. We have also discussed novel treatment approaches and highlighted areas of future research.

36. Commercially available immunoglobulins contain virus neutralizing antibodies against all major genotypes of polyomavirus BK.
Am J Transplant. 2015 Apr;15(4):1014-20.
Pastrana DV, Zeng G, Huang Y, et al.

ABSTRACT
Neutralizing antibodies (NAbs) form the basis of immunotherapeutic strategies against many important human viral infections. Accordingly, we studied the prevalence, titer, genotype-specificity, and mechanism of action of anti-polyomavirus BK (BKV) NAbs in commercially available human immune globulin (IG) preparations designed for intravenous (IV) use. Pseudovirions (PsV) of genotypes Ia, Ib2, Ic, II, III, and IV were generated by co-transfecting a reporter plasmid encoding luciferase and expression plasmids containing synthetic codon-modified VP1, VP2, and VP3 capsid protein genes into 293TT cells. NAbs were measured using luminometry. All IG preparations neutralized all BKV genotypes, with mean EC50 titers as high as 254 899 for genotype Ia and 6,666 for genotype IV. Neutralizing titers against genotypes II and III were higher than expected, adding to growing evidence that infections with these genotypes are more common than currently appreciated. Batch to batch variation in different lots of IG was within the limits of experimental error. Antibody mediated virus neutralizing was dose dependent, modestly enhanced by complement, genotype-specific, and achieved without effect on viral aggregation, capsid morphology, elution, or host cell release. IG contains potent NAbs capable of neutralizing all major BKV genotypes. Clinical trials based on sound pharmacokinetic principles are needed to explore prophylactic and therapeutic applications of these anti-viral effects, until effective small molecule inhibitors of BKV replication can be developed.

37. Antigen-Specificity of T Cell Infiltrates in Biopsies With T Cell-Mediated Rejection and BK Polyomavirus Viremia: Analysis by Next Generation Sequencing.
Am J Transplant. 2016 Nov;16(11):3131-3138.
Zeng G., Huang Y., Huang Y., et al.

ABSTRACT
This study interrogates the antigen-specificity of inflammatory infiltrates in renal biopsies with BK polyomavirus (BKPyV) viremia (BKPyVM) with or without allograft nephropathy (BKPyVN). Peripheral blood mononuclear cells (PBMC) from five healthy HLA-A0101 subjects were stimulated by peptides derived from the BKPYV proteome or polymorphic regions of HLA. Next generation sequencing of the T cell-receptor complementary DNA was performed on peptide-stimulated PBMC and 23 biopsies with T cell-mediated rejection (TCMR) or BKPyVN. Biopsies from patients with BKPyVM or BKVPyVN contained 7.7732 times more alloreactive than virus-reactive clones. Biopsies with TCMR also contained BKPyV-specific clones, presumably a manifestation of heterologous immunity. The mean cumulative T cell clonal frequency was 0.1378 for alloreactive clones and 0.0375 for BKPyV-reactive clones. Samples with BKPyVN and TCMR clustered separately in dendrograms of V-family and J-gene utilization patterns. Dendrograms also revealed that V-gene, J-gene, and D-gene usage patterns were a function of HLA type. In conclusion, biopsies with BKPyVN contain abundant allospecific clones that exceed the number of virus-reactive clones. The T cell component of tissue injury in viral nephropathy appears to be mediated primarily by an "innocent bystander" mechanism in which the principal element is secondary T cell influx triggered by both antiviral and anti-HLA immunity.

38. Observations on the use of cidofovir for BK virus infection in renal transplantation

Transpl Infect Dis 2014: 16: 975–983

Kuten, S. A., Patel, S. J., Knight, R. J. et al.

ABSTRACT

Background: In renal transplantation, BK virus infection can result in significant graft nephropathy and loss. While reduction in immunosuppression (IS) is considered standard therapy, adjunct agents may be warranted. Data are suggestive of a possible role of cidofovir for the management of BK. This study aims to describe the course of BK viremia (BKV) in a large cohort of renal transplant patients receiving adjunct cidofovir.

Methods: We evaluated kidney and kidney-pancreas recipients who received cidofovir combined with reduced IS for management of high-level BKV or BK virus nephropathy (BKVN). We examined the rate and timing of BKV clearance, and performed a multivariate analysis to identify risk factors associated with long-term (>6 months) viremia.

Results: In total, 75 patients received a median of 13 doses of cidofovir in conjunction with reduced IS; 32 patients (43%) had shortterm BKV (≤6 months), and 43 (57%) had long-term BKV. Overall, 53 of 75 patients (71%) eventually cleared BKV at a median of 4.2 months (interquartile range 2.1–9.3 months). Independent factors associated with long-term BKV included older age (odds ratio [OR] 1.1, P = 0.02), delayed graft function (OR 31.4, P = 0.01), and higher peak BKV (OR 12.8, P = 0.02), while BKV reduction by at least 1 log10copies/mL at 1 month of treatment was associated with clearance within 6 months (OR 49.3, P < 0.01). Patients with earlier clearance maintained stable graft function and no graft losses, while long-term BKV was associated with a 15% decline in estimated glomerular filtration rate.

Conclusions: Adjunct cidofovir resulted in preservation of renal function when viral clearance occurred within 6 months of initiation. This retrospective review defines factors predicting response to cidofovir in conjunction with reduced IS for BKVN or high-level BKV. Still, considering cost, frequency of administration, and treatment duration, a randomized trial is necessary to define the exact utility of cidofovir in the setting of BK virus infection.

39. BK Polyomavirus Infection and Renourinary Tumorigenesis.
Am J Transplant. 2016 Feb;16(2):398-406. doi: 10.1111/ajt.13550. Epub 2016 Jan 5. Review. Erratum in: Am J Transplant. 2017 Jan;17 (1):308.
Papadimitriou JC., Randhawa P., Rinaldo CH. et al.

ABSTRACT
BK polyomavirus (BKPyV) infection represents a major problem in transplantation, particularly for renal recipients developing polyomavirus-associated nephropathy (PyVAN). The possibility that BKPyV may also be oncogenic is not routinely considered. Twenty high-grade renourinary tumors expressing polyomavirus large T antigen in the entirety of the neoplasm in 19 cases, including the metastases in six, have been reported in transplant recipients with a history of PyVAN or evidence of BKPyV infection. Morphological and phenotypical features consistent with inactivation of the tumor suppressors pRB and p53 were found in the bladder tumors, suggesting a carcinogenesis mechanism involving the BKPyV large tumor oncoprotein/antigen. The pathogenesis of these tumors is unclear, but given the generally long interval between transplantation and tumor development, the risk for neoplasms after BKPyV infections may well be multifactorial. Other elements potentially implicated include exposure to additional exogenous carcinogens, further viral mutations, and cell genomic instability secondary to viral integration, as occurs with the Merkel cell PyV-associated carcinoma. The still scarce but increasingly reported association between longstanding PyVAN and renourinary neoplasms requires a concerted effort from the transplant community to better understand, diagnose, and treat the putative association between the BKPyV and these neoplasms.

40. CMV and BKPyV Infections in Renal Transplant Recipients Receiving an mTOR Inhibitor-Based Regimen Versus a CNI-Based Regimen: A Systematic Review and Meta-Analysis of Randomized, Controlled Trials.

Clin J Am Soc Nephrol. 2017 Jun 2.

Mallat SG., Tanios BY., Itani HS. et al.

ABSTRACT

Background and objectives: The objective of this meta-analysis is to compare the incidences of cytomegalovirus and BK polyoma virus infections in renal transplant recipients receiving a mammalian target of rapamycin inhibitor (mTOR)-based regimen compared with a calcineurin inhibitor-based regimen.

Design, setting, participants, & measurements: We conducted a comprehensive search for randomized, controlled trials up to January of 2016 addressing our objective. Other outcomes included acute rejection, graft loss, serious adverse events, proteinuria, wound-healing complications, and eGFR. Two review authors selected eligible studies, abstracted data, and assessed risk of bias. We assessed quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation methodology.

Results: We included 28 randomized, controlled trials with 6211 participants classified into comparison 1: mTOR inhibitor versus calcineurin inhibitor and comparison 2: mTOR inhibitor plus reduced dose of calcineurin inhibitor versus regular dose of calcineurin inhibitor. Results showed decreased incidence of cytomegalovirus infection in mTOR inhibitor-based group in both comparison 1 (risk ratio, 0.54; 95% confidence interval, 0.41 to 0.72), with high quality of evidence, and comparison 2 (risk ratio, 0.43; 95% confidence interval, 0.24 to 0.80), with moderate quality of evidence. The available evidence neither confirmed nor ruled out a reduction of BK polyoma virus infection in mTOR inhibitor-based group in both comparisons. Secondary outcomes revealed more serious adverse events and acute rejections in mTOR inhibitor-based group in comparison 1 and no difference in comparison 2. There was no difference in graft loss in both comparisons. eGFR was higher in the mTOR inhibitor-based group in comparison 1 (mean difference =4.07 ml/min per 1.73 m2; 95% confidence interval, 1.34 to 6.80) and similar to the calcineurin inhibitor-based group in comparison 2. More proteinuria and wound-healing complications occurred in the mTOR inhibitor-based groups.

Conclusions: We found moderate- to high-quality evidence of reduced risk of cytomegalovirus infection in renal transplant recipients in the mTOR inhibitor-based compared with the calcineurin inhibitor-based regimen. Our review also suggested that a combination of a mTOR inhibitor and a reduced dose of calcineurin inhibitor may be associated with similar eGFR and rates of acute rejections and serious adverse events compared with a standard calcineurin inhibitor-based regimen at the expense of higher incidence of proteinuria and wound-healing complications.

41. Correlation of BK Virus Neutralizing Serostatus With the Incidence of BK Viremia in Kidney Transplant Recipients

Transplantation: June 2017 - Volume 101 - Issue 6 - p 1495–1505

Abend JR., Changala M., Sathe A. et al

ABSTRACT

Background: BK virus (BKV)-associated nephropathy is the second leading cause of graft loss in kidney transplant recipients. Due to the high prevalence of persistent infection with BKV in the general population, it is possible that either the transplant recipient or donor may act as the source of virus resulting in viruria and viremia. Although several studies suggest a correlation between donor-recipient serostatus and the development of BK viremia, specific risk factors for BKV-related complications in the transplant setting remain to be established.

Methods: We retrospectively determined the pretransplant BKV neutralizing serostatus of 116 donors (D)-recipient (R) pairs using infectious BKV neutralization assays with representatives from the 4 major viral serotypes. The neutralizing serostatus of donors and recipients was then correlated with the incidence of BK viremia during the first year posttransplantation.

Results: There were no significant differences in baseline demographics or transplant data among the 4 neutralizing serostatus groups, with the exception of calculated panel-reactive antibody which was lowest in the D+/R− group. Recipients of kidneys from donors with significant serum neutralizing activity (D+) had elevated risk for BK viremia, regardless of recipient serostatus (D+ versus D−: odd ratio, 5.0; 95% confidence interval, 1.9-12.7]; P = 0.0008). Furthermore, donor-recipient pairs with D+/R− neutralizing serostatus had the greatest risk for BK viremia (odds ratio, 4.9; 95% confidence interval, 1.7-14.6; P = 0.004).

Conclusions: Donor neutralizing serostatus correlates significantly with incidence of posttransplant BK viremia. Determination of donor-recipient neutralizing serostatus may be useful in assessing the risk of BKV infection in kidney transplant recipients.

42. Polyomavirus Replication and Smoking Are Independent Risk Factors for Bladder Cancer After Renal Transplantation

Transplantation: June 2017 - Volume 101 - Issue 6 - p 1488–1494

Liu Sandy, Chaudhry Muhammad R., Berrebi Alexander A et al.

ABSTRACT

Background**: Solid organ transplant recipients are at increased risk for developing malignancies.** Polyomaviruses (PV) have been historically associated with experimental tumor development and recently described in association with renourinary malignancies in transplant patients. The aim of this study was to investigate the relationship between PV replication and smoking, and the development of malignant neoplasms in kidney transplant recipients.

Methods: A retrospective case-control study was conducted for PV replication in all kidney biopsies and urine cytologies performed between 1998 and 2014 from kidney transplant recipients at the University of Maryland Medical Center. Polyomavirus-positive patients (n = 943) were defined as having any of the following: a kidney biopsy with PV associated nephropathy, any urine cytology demonstrating “decoy” cells, and/or significant polyomavirus BK viremia. Polyomavirus-negative matched patients (n = 943) were defined as lacking any evidence of PV replication. The incidence of malignancy (excluding nonmelanoma skin tumors) was determined in these 1886 patients and correlated with demographic data and history of smoking.

Results: There was a 7.9% incidence of malignant tumors after a mean posttransplant follow-up of 7.9 ± 5.4 years. Among all cancer subtypes, only bladder carcinoma was significantly associated with PV replication. By multivariate analysis, only PV replication and smoking independently increased the risk of bladder cancer, relative risk, 11.7 (P = 0.0013) and 5.6 (P = 0.0053), respectively.

Conclusions: The findings in the current study indicate that kidney transplant recipients with PV replication and smoking are at particular risk to develop bladder carcinomas and support the need for long-term cancer surveillance in these patients.

43. Stabilization of renal function after the first year of follow-up in kidney transplant recipients treated for significant BK polyomavirus infection or BK polyomavirus-associated nephropathy
Transpl Infect Dis. 2017;e12681.
Simard-Meilleur M-Ch., Bodson-Clermont P., St-Louis G. et al.

ABSTRACT
Background: BK polyomavirus virus (BKPyV) screening and immunosuppression reduction effectively prevent graft loss due to BKPyV-associated nephropathy (BKPVAN) during the first year after transplantation. The aim of our study was to evaluate the impact of this infection during longer follow-up periods.
Methods: We reviewed the outcome of our screening and immunosuppression reduction protocol in 305 patients who received a kidney transplant between March 2008 and January 2013. Quantitative BKPyV DNA surveillance in plasma was performed at 1, 2, 3, 6, 9, and 12 months after transplantation. Patients with significant viremia and/or biopsy-proven BKPVAN were treated with immunosuppression reduction and leflunomide.
Results: During the first post-transplant year, 24 patients (7.9%) developed significant viremia at a median time of 95 days, and 18 patients had BKPVAN; 23 of the 24 (7.5%) were treated according to our protocol (group BKV+); 225 patients (73.8%) did not develop any BK viremia (group BKV−). Allograft function was similar in both groups at 1 month post transplantation (P=.87), but significantly worse at 1 year in the BKV+ group (P=.002). Thereafter, kidney function stabilized in the BKV+ group and no differences in patient and graft survival were seen between the groups after a median follow-up of 4 years.
Conclusions: We confirm the early occurrence of BKPyV replication after transplantation and the short-term decline in renal function. However, early detection of BKPyV replication, prompt diagnosis, and reduction in immunosuppression may offer long-term benefits for graft function.

44. The Loss of BKV-Specific Immunity From Pretransplantation to Posttransplantation Identifies Kidney Transplant Recipients at Increased Risk of BKV Replication.
American Journal of Transplantation 2015; 15: 2159–2169
Schachtner T., Stein M., Babel N. et al.

ABSTRACT
Quantification of BKV-load and BKV-specific immunity have been evaluated to monitor BKV-replication and outcomes in kidney transplant recipients (KTRs) with BKV-infection. However, it remains crucial to better understand how immune markers can predict the risk for later infection. We studied all KTRs between 2008 and 2011. Twenty-four KTRs were diagnosed with BKV-replication and a control group of 127 KTRs was used for comparison. Samples were collected before at +1,+2, and +3 months posttransplantation. BKV-specific and alloreactive T cells were measured using an interferon-g Elispot assay. The extent of immunosuppression was quantified by lymphocyte subpopulations and interferon-gamma levels. KTRs with a loss of BKV-specific T cells directed to Large T-antigen from pretransplantation to posttransplantation were at increased risk of BKV-replication ($p<0.001$). In contrast, KTRs with stable/ rising BKV-specific T cells were more likely not to develop BKV-replication ($p<0.05$). KTRs developing BKV-replication showed significantly lower CD3+, CD4+, CD8+ T cells and interferon-γ levels posttransplantation, but significantly higher alloreactive T cells ($p<0.05$). Monitoring pretransplant and posttransplant BKV-specific T cells is suggested a sensitive marker to identify KTRs at increased risk of BKV-replication. Increased susceptibility to immunosuppression predisposes KTRs to a loss of protective BKV-specific immunity that results in impaired virus control and BKV-replication.