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BK virus infections in renal transplant recipients

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The BK virus is a member of the polyomavirus family. Infections with BK virus are widespread with a seroprevalence of around 80% in the general population. Following an asymptomatic primary infection, BK virus remains latent in healthy subjects. Reactivation occurs in immunocompromised patients. BK virus is pathogenic mainly among patients who have received a kidney transplant, in whom the virus can cause specific tubulo-interstitial nephritis and even result in graft failure among approximately 20–30% of nephritic cases. The cornerstone of BK virus infection or BK virus-associated nephropathy treatment is to decrease the immunosuppressive regimen, which must then be offset with the risk of rejection. BK Virus Nephropathy (BKVN) occurs in up to 10% of renal transplant recipients (RRT) and can result in graft loss in up to 50% of those affected.

In this study, we retrospectively analyzed the presence of BK virus in plasma and urine samples of patients applied to the Nephrology Clinic of our hospital between 2010–2015. BK virus DNA was determined by real-time PCR using artus BK virus RG PCR kit (Qiagen, Germany) on the Rotor-Gene system (Corbett Research, Australia). The analytical sensitivity of the kit is 0.195 copies/μl according to the user manual.

A total of 243 samples (urine and plasma) from 131 patients (69 male, 62 female), ages ranging from 20 to 72 were enrolled. BK virus DNA was detected in 56 (38.6%) urine samples and in 27 (13.1%) plasma samples. In 19 simultaneously sent urine and plasma sample pairs of 13 patients, BK virus DNA was positive. The minimum and maximum DNA levels of positive urine and plasma samples were as 4–1.4 × 10^4 copies/ml and 6–5.3 × 10^4 copies/ml respectively.

In conclusion quantititative viral load monitoring for BK virus (BKV) in urine and plasma samples by real-time PCR is an important tool in the management of polyomavirus associated nephropathy in renal transplant patients.

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The impact of viral respiratory infections in the first year post-transplant period of pediatric hematopoietic stem cell transplantation (HSCT) recipients

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Background: Infection caused by respiratory viruses (RV) is a threat for hematopoietic stem cell transplant (HSCT) recipients. RVs in HSCT patients with respiratory syndromes should be strictly monitored in the pre-engraftment or early post-transplantation period and in patients with acute or chronic GVHD. Due to the high morbidity and mortality rates associated with RVs infections and the lack of directed antiviral therapy for most of these infections, prevention remains the mainstay for reducing their incidence and controlling transmission in HCT recipients. This retrospective study aimed to investigate the incidence and the duration of respiratory episodes caused by viruses in pediatric HSCT recipients.

Material and methods: Patients who underwent allogeneic or autologous HSCT at Pediatric Hematology–Oncology Unit, Fondazione IRCCS Policlinico San Matteo, Pavia from January 2010 to December 2014 were analyzed. Respiratory samples from patients with respiratory syndromes were routinely tested using a panel of RT-PCR and real-time RT-PCR assays for 12 respiratory viruses within the first year post-transplant.

Results: One hundred eighty-six HSCT recipients including 158 (84.9%) allogeneic (80 MUD, 56 PMFD, 21 MFD, and 1 sibling) and 28 (15.1%) autologous transplants were evaluated. In 118/186 (63.4%) patients at least one respiratory episode caused by viruses was identified, while 68/186 (36.6%) patients were negative. Among positive patients, 73/118 (61.9%) had a single viral respiratory episode, while 45/118 (38.1%) had multiple episodes (29 with 2 episodes, 8 with 3, 8 with 4 and 1 with 6). In patients with multiple viral episodes, the first episode was observed significantly earlier (median 17.5 days; range 1–349 days) than patients experiencing a single viral episode (median 62 days; range 1–358 days; p = 0.01). A total of 192 viral episodes, including 174 (90.6%) single infections and 18 (9.4%) co-infections were observed. Among episodes sustained by a single virus, HRVs were the most prevalent viruses with 54.0% followed by respiratory syncytial virus (13.2%), human coronaviruses (9.2%), human parainfluenza viruses (8.0%), influenza A (6.3%), adenovirus (6.3%), and influenza B (2.9%). Twenty-seven episodes (14.0% of total) of prolonged infections defined as viral shedding ≥30 days were observed. The median duration of viral shedding was 64 days (range 30–159 days). In 18/27 (66.6%) patients, the onset of infection occurred during the induction and before transplant engraftment (<30 days from TX). In these patients, the duration of viral episodes was higher than those observed in the remaining 9 patients, in which the onset
of infections occurred after the engraftment (>30 days from TX) \((p = 0.02)\).

**Conclusions:** Among pediatric HSCT recipients, viral respiratory infections in the post-transplant period are frequent and sometimes prolonged. Preventive measures must be tightened in this population in order to reduce the derived morbidity and mortality.

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**Normalizing ELISPOT to quantify human cytomegalovirus (HCMV) and Epstein Barr-virus (EBV) specific T-cell response in kidney transplant recipients**

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**Background:** Herpes virus infection or reactivation are major complications in solid organ transplant recipients. Virus-specific T-cell response is crucial to control infection.

**Methods:** HCMV and EBV specific CD4+ and CD8+ T-cell response were investigated in 29 kidney transplant recipients by a novel approach of enzyme-linked immunospot assay (ELISPOT). Overlapping 15-mer peptide pools of HCMV proteins immediate early IE-1, IE-2 and phosphoprotein pp65, and of EBV lytic (BZLF1 and BMRF1) and latent (EBNA1, EBNA3a, EBNA3b, EBNA3c, LMP1 and LMP2) proteins were used for stimulation of both CD4+ and CD8+ HCMV-specific and EBV specific T-cells, respectively. Virological and immunological monitoring were performed for one year of follow-up.

**Results:** As for HCMV infection, 13/19 (68.4%) HCMV seropositive recipients showed levels of HCMV replication <100,000 DNA copies/ml blood and did not require anti-viral treatment, while 6/19 (31.6%) HCMV-seropositive patients were treated since showing ≥100,000 HCMV DNA copies/ml blood. Patients with spontaneous control of infection showed, at 120 days after transplant, levels of HCMV specific CD4+ T-cells significantly higher with respect to patients who needed treatment. HCMV specific T-cell response to single HCMV proteins (pp-65, IE-1, IE-2) was examined: pretransplant number of both CD4+ and CD8+ specific T cells directed against IE-1 showed significantly higher level in patients controlling infection and their level remained significantly higher until 120 days. No difference was shown for pp-65 and IE-2 between the two groups of patients. In addition, 5 HCMV-seronegative recipients receiving organ from HCMV seropositive donor (D+/R−), were examined: 4/5 developed a primary infection within one month from transplantation and required antiviral treatment. HCMV-specific CD4+ T-cells remained significant lower with respect to patients able to control infection until 120 days after transplantation.

As for EBV infection, 3/29 (10.3%) EBV-seropositive patients reaching levels of EBV ≥10,000 DNA copies/ml blood did not showed EBV-specific T-cell response for the entire period considered. However, EBV-specific T-cell response was detected in only 8/20 (40%) patients examined at 1 year follow-up, regardless of the presence of EBV DNA in blood.

**Conclusions:** Normalizing ELISPOT may be a simple and useful tool to perform immunological monitoring in solid organ transplant recipients and to detect herpes virus specific response. However, while the importance of HCMV-specific T-cell response to control HCMV infection is evident, further studies are required to better define the role of EBV-specific T-cell response.

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**BK polyomavirus-seroreactivity increases with virus replication**

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**Background:** BK polyomavirus (BKVpyV) infection causes nephropathy in 1–10% of kidney transplant recipients. This condition results in graft–loss in up to 50% of cases unless immunosuppression is lowered. Specific antiviral treatment is not available. In immunocompetent individuals, BKPyV resides latently in kidney tubular epithelium after primary infection during childhood.

In order to predict which recipients will develop BKPyV nephropathy, we recently analyzed a cohort of kidney donor-recipient pairs prior to transplantation for several immunological and virological parameters. That study showed a strong correlation between the strength of BKPyV-seroreactivity measured in the donor and BKPyV infection and nephropathy in the recipient [1]. We hypothesized that BKPyV-seroreactivity of the donors mirrors the load of infectious virus in the transplanted kidney. To further investigate the relation between BKPyV-seroreactivity and BKPyV-replication, we analyzed the dynamics of BKPyV-seroreactivity in individuals that did or did not experienced a detectable BKPyV infection.

**Methods:** A group of 101 kidney transplant recipients was analyzed for BKPyV-seroreactivity (VP1-antigen; Luminex immunoassay) and for BKPyV viremia (viral load measured by q-PCR). Serum and blood plasma samples were obtained before transplantation and at 3-month intervals until 18 months after. As controls 87 healthy blood donors were analyzed with a 12-month interval. Descriptive statistics and mixed model analysis was used to analyze the association between measured peak BKPyV-loads and BKPyV-IgG seroreactivity.

**Results:** At baseline the overall BKPyV-seropositivity was high in both transplant recipients (92%) and blood donors (99%). The mean baseline BKPyV-IgG level in both groups was comparable. In 85% of the kidney recipients, BKPyV viremia was detected at some point during follow-up, with peak viral loads ranging from 10 to 579700 copies/ml, while no viremia was detected in the blood donors. After a year, in the healthy blood donors, the mean level of seroreactivity remained the same \((p = 0.929)\). This was also the case among kidney recipients without BKPyV viremia \((p = 0.981)\). Among kidney recipients that did develop viremia, however, a statistically significant increase in BKPyV-seroreactivity was observed.