

CHAPTER 7.3 BK Polyomavirus and JC Polyomavirus infection

Lars Pape¹ & Burkhard Tönshoff²

¹ Department of Paediatrics II, University Hospital of Essen, Essen, Germany

² Heidelberg University, Medical Faculty Heidelberg, Department of Paediatrics I, University Children's Hospital, Heidelberg, Germany

ORCIDiDs:

Lars Pape: <https://orcid.org/0000-0002-3635-6418>

Burkhard Tönshoff: <https://orcid.org/0000-0002-6598-6910>

1 Introduction

After kidney transplantation, immunosuppressive treatment disturbs the individual balance between virus replication and cellular immune response, resulting in an increased incidence of severe viral complications. After primary infection mainly during childhood, BK polyomavirus (BKPyV) persists in the renourinary tract. While BKPyV infection occurs without apparent signs or symptoms in healthy individuals, BKPyV causes BKPyV-associated nephropathy (BKPyVAN) in 1% to 10% of all kidney transplant recipients, leading to premature graft failure in 10–80% [1–7]. Recently, new guidelines for the management of BKPyV after kidney transplantations have been published [8]. This text summarises the most important paediatric aspects of this guideline.

2 Definition of BKPyV nephropathy

- *Probable* BKPyV nephropathy – plasma BKPyV DNAemia > 1000 c/mL (or equivalent) persisting for > 2 weeks
- *Presumptive* BKPyV nephropathy – plasma BKPyV DNAemia > 10,000 c/mL (or equivalent)
- *Proven* BKPyV nephropathy – detection of compatible cytopathic effects in a graft biopsy plus immunohistochemistry and a specific diagnostic test that identifies BKPyV as opposed to JC polyomavirus (JCPyV)

3 Risk factors for BKPyV DNAemia

- Younger recipient age
- Obstructive uropathy
- Zero HLA-DR match
- Lymphocyte depleting induction therapy
- Tacrolimus-based immunosuppressive therapy

4 Diagnostic recommendations

- For paediatric kidney transplant recipients, we recommend monthly screening for plasma BKPyV DNAemia until month 9, then every 3 months until month 36
- In paediatric kidney transplant recipients with BKPyV DNAemia, we recommend that a kidney biopsy be performed if clinically indicated (e.g., increase in serum creatinine, proteinuria, haematuria).
- In paediatric kidney transplant recipients with stable kidney function and persistent BKPyV DNAemia > 10,000 c/mL (*or equivalent*) despite reducing immunosuppression, we suggest performing a renal allograft biopsy.
- In paediatric kidney transplant recipients with stable kidney function, persistent BKPyV DNAemia and increased immunological risk (e.g. ABO incompatible kidney transplantation, HLA-DSA, re-transplantation, poor adherence, multi-organ transplant, history of previous rejection) or virological risk (e.g. graft loss due to BKPyV nephropathy), we suggest performing a renal allograft biopsy to exclude subclinical rejection before reducing immunosuppression.

5 Treatment recommendations

- Start treatment if of BKPyV DNA 1000–10.000 c/mL twice or > 10.000 c/mL
- We recommend reduction of maintenance immunosuppression as the primary treatment of persistent BKPyV DNAemia, presumptive or proven BKPyV nephropathy in paediatric kidney transplant patients without concurrent acute rejection. See below for details:

- We suggest measurement of plasma creatinine and BKPyV DNA aemia every 1–2 weeks during taper of immunosuppression.
- We suggest re-increasing of immunosuppression after sustained clearance of BKPyV DNAemia.
- We suggest monthly monitoring of BKPyV DNAemia for 3 months in the event of re-increasing immunosuppression because of rejection therapy.
- We do not recommend adjunctive therapies including leflunomide, cidofovir and fluoroquinolones due to the lack of well-designed studies that were confounded by concomitant reduction in immunosuppression.

Reduction of immunosuppression in case of (presumptive) BKPyVAN

- We suggest first confirming that all immunosuppressive drug doses and concentrations are within the institutional target range.
- We recommend monitoring for BKPyV DNAemia every 2–4 weeks until clearance.

Strategy 1: Antimetabolite is reduced first

- I. Reduce the antimetabolite dose by at least 50%.
We suggest further reduction of immunosuppression if BKPyV DNAemia does *not* decrease by 10-fold or does *not* clear below the lower limit of detection (weak, low) after 4 weeks, as follows:
- II. Discontinue the antimetabolite and taper the corticosteroid dose to 5–10 mg/1.73 m² per day of prednisone or equivalent, if applicable.
For patients not on corticosteroids, we suggest a maintenance dose of 5–10 mg/1.73 m² per day of prednisone or equivalent to avoid CNI monotherapy.
- III. If further reduction in immunosuppression is required, we suggest a step-wise reduction of the calcineurin inhibitor dose (tacrolimus trough target 5 ng/mL; cyclosporine trough target 100 ng/mL)
Target concentrations for further reductions are not well described and need to be individualised. Expert opinion and case reports discuss a tacrolimus target trough concentration of 3 ng/mL and a cyclosporine target trough concentration of 75 ng/mL, followed by a tacrolimus target trough of 1.5 ng/mL and a cyclosporine target trough of 50 ng/mL.

Strategy 2: Calcineurin inhibitor is reduced first

- I. Reduce calcineurin inhibitor dose by 25–50% in one or two steps to target trough concentrations of tacrolimus of 3–5 ng/mL and cyclosporine trough concentrations of 75–125 ng/mL)

We suggest further reduction of immunosuppression if BKPyV DNAemia does *not* decrease by 10-fold or fall below the lower limit of detection after 4 weeks as follows:

- II. Reduce the antimetabolite by 50% and taper the corticosteroid dose to 5–10 mg/1.73 m² per day of prednisone or equivalent, if applicable.
III. Antimetabolite discontinuation

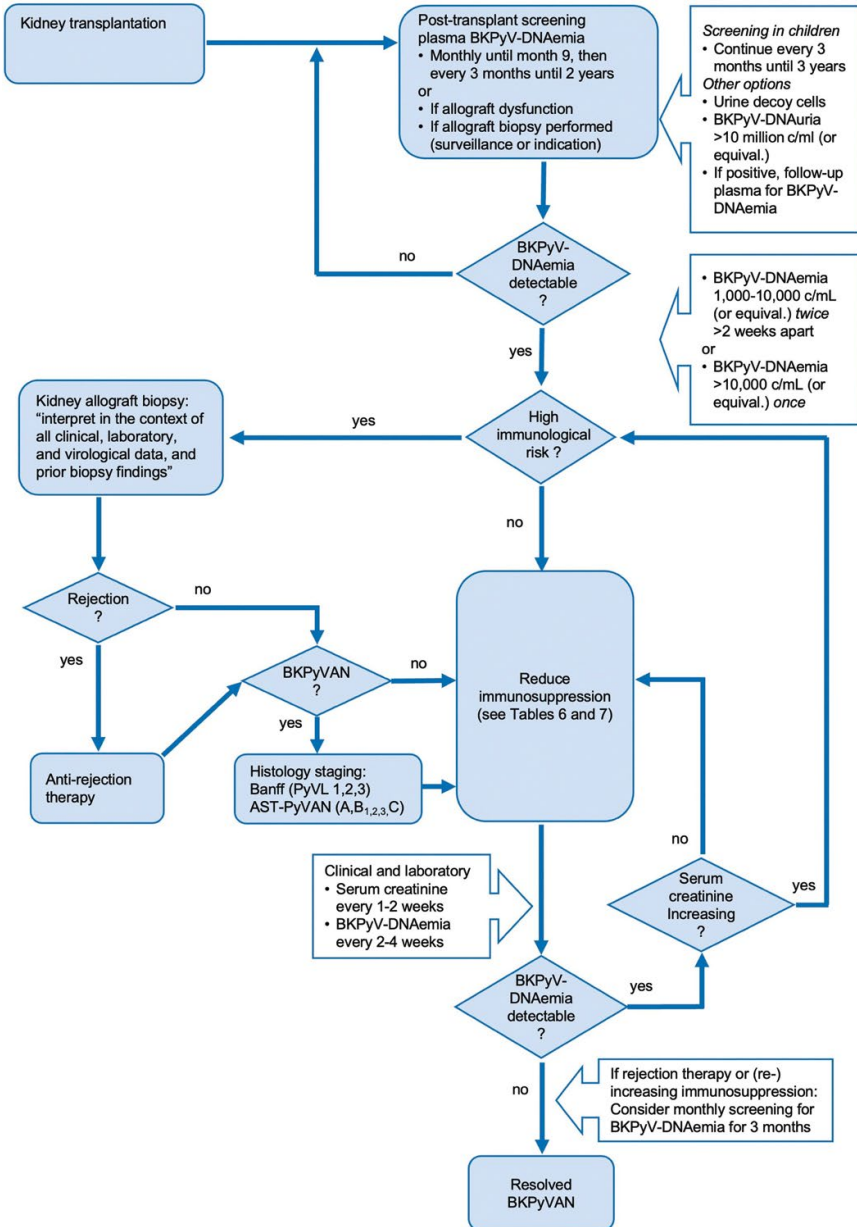
We suggest a maintenance dose of 5–10 mg/1.73 m² per day of prednisone or equivalent for patients who are not on corticosteroids to avoid CNI monotherapy.

Target concentrations for further reduction are poorly described and need to be individualised. Expert opinion and case reports suggest target concentrations of 3 ng/mL for tacrolimus and target concentrations of 75 ng/mL for cyclosporine, followed by next steps of 1.5 ng/mL and 50 ng/mL, respectively.

6 JC Polyomavirus nephropathy

As JC polyomavirus (JCPyV) nephropathy is very rare, universal screening as for BKPyV is not recommended. The diagnosis of JCPyV nephropathy should be suspected in biopsies detecting LTag expression using the cross-reacting SV40-LTag antibody in a kidney transplant recipient without detectable BKPyV DNAemia or high-level BKPyV DNAuria [12]. Morphologically, BKPyV and JCPyV nephropathy are indistinguishable. The specific diagnosis of JCPyV nephropathy requires immunohistochemistry staining with JCPyV-specific antibodies, such as those raised against the JCPyV major capsid Vp1 protein or in situ hybridisation with JCPyV-specific probes. Another approach is to determine the tissue viral load of JCPyV-DNA in biopsy material by (semi-)quantitative molecular testing, whereby BKPyV DNA should not be detectable. Kidney transplant patients with JCPyV nephropathy are characterised by high urinary JCPyV loads of >10 million c/mL (or equivalent), while urinary BKPyV loads are low or undetectable. In contrast to BKPyV screening, plasma JCPyV loads are not a reliable marker for screening, diagnosis, or monitoring of JCPyV nephropathy, as they are usually undetectable or low.

7.3 BK Polyomavirus and JC Polyomavirus infection



TRANSPLANTATION

References

- 1 Leuzinger K, Hirsch HH. 2023. Human polyomaviruses, p 2093–2130. In Carroll KC, Pfaller MA (ed), *Manual of Clinical Microbiology*, 13th ed. ASM Press, Washington, DC.
- 2 Hirsch HH. 2023. Polyomaviruses, p 2227–2233. In Goldman L, Cooney KA (ed), *Goldman-Cecil Medicine*, 27th ed, vol 2. Elsevier, Philadelphia, PA.
- 3 Hirsch HH, Knowles W, Dickenmann M, Passweg J, Klimkait T, Mihatsch MJ, Steiger J. 2002. Prospective study of polyomavirus type BK replication and nephropathy in renal-transplant recipients. *N Engl J Med* 347:488–496.
- 4 Jiang D, Mantas A, Studier-Fischer A, Fuchs J, Uluk D, Loos M, Mieth M, Zeier M, Husen P, Golriz M, Kahlert C, Ryschich E, Mehrabi A, Pratschke J, Michalski CW, Czigany Z. 2024. *Clinical Research in Renal Transplantation: A Bibliometric Perspective on a Half-century of Innovation and Progress*. *Transplantation* doi:10.1097/TP.0000000000004887.
- 5 Kaminski MM, Abudayyeh OO, Gootenberg JS, Zhang F, Collins JJ. 2021. CRISPR-based diagnostics. *Nat Biomed Eng* 5:643–656.
- 6 Hirsch HH, Mengel M, Kamar N. 2022. BK Polyomavirus Consensus. *Clin Infect Dis* 75:2046–2047.
- 7 Höcker B, Schneble L, Murer L, et al. Epidemiology of and Risk Factors for BK Polyomavirus Replication and Nephropathy in Pediatric Renal Transplant Recipients: An International CERTAIN Registry Study. *Transplantation*. 2019;103(6):1224–1233
- 8 Kotton CN, Kamar N, Wojciechowski D, Eder M, Hopfer H, Randhawa P, Sester M, Comoli P, Tedesco Silva H, Knoll G, Brennan DC, Trofe-Clark J, Pape L, Axelrod D, Kiberd B, Wong G, Hirsch HH, Transplantation Society International BK Polyomavirus Consensus Group. 2024. The Second International Consensus Guidelines on the Management of BK Polyomavirus in Kidney Transplantation. *Transplantation* 2024;108(9):1834–1866
- 9 Ahlenstiel-Grunow T, Pape L. Diagnostics, treatment, and immune response in BK polyomavirus infection after pediatric kidney transplantation. *Pediatr Nephrol*. 2020 Mar;35(3):375–382.
- 10 Ahlenstiel-Grunow T, Pape L. Immunosuppression, BK polyomavirus infections, and BK polyomavirus-specific T cells after pediatric kidney transplantation. *Pediatr Nephrol*. 2020 Apr;35(4):625–631.

- 11 Fichtner A, Schmidt J, Süsal C, et al. Risk of cellular or antibody-mediated rejection in pediatric kidney transplant recipients with BK polyomavirus replication – an international CERTAIN registry study. *Pediatr Nephrol.* 2024 Oct 11. doi: 10.1007/s00467-024-06501-7. Online ahead of print.
- 12 Höcker B, Tabatabai J, Schneble L, et al. JC polyomavirus replication and associated disease in pediatric renal transplantation: an international CERTAIN Registry study. *Pediatr Nephrol.* 201833(12):2343–2352.