BK virus nephropathy in kidney transplant recipients

Hannah Imlay, MD MS

BK Polyomavirus (BKPyV)

- Cause of BKPyV associated nephropathy (BKPyVAN)
- Important cause of allograft dysfunction and loss
  - Need for effective, evidence-based prevention and therapy
- Limitations in clinical trials:
  - Low incidence of biopsy-proven disease
  - Allograft biopsy is invasive and sometimes infeasible
  - Limitations in sensitivity of gold standard diagnosis (allograft biopsy)

Establishing a surrogate marker of BKPyVAN would improve sensitivity of endpoints and feasibility of clinical trials

Current clinical guidelines

- Variation in use of probable or presumed definitions of BKPyVAN based on viral load
  - Some use DNAemia as a surrogate marker, but no measures of allograft dysfunction
  - Lack of standardization in BKPyV viral load diagnostics
- Furthermore, there exist variation in clinical definitions of proven disease

Consensus group	Proven BKPyVAN	Probable/Presumptive BKPyVAN
American Society of Transplantation Infectious Diseases Community of Practice (AST)	Demonstration of cytopathic changes of tubular epithelial cells in the allograft tissue, confirmed by IHC or ISH.	Probable: plasma DNA load >3 log10 in two measurements within 3 weeks Presumptive: plasma DNA load >4 log10 in at least one of two measurements
European renal association – European dialysis and transplant association (ERA-EDTA)	Demonstration of viral cytopathic changes and antibodies against SV40 in kidney biopsy	N/A
American Society of Nephrology (ASN)	N/A	Plasma BKPyV load ≥10,000 copies/mL in at least one measurement
The Renal Association	Demonstration of virus in renal tissue, usually by staining with antibody for large T antigen of SV40	N/A
Banff Working Group	Morphologic evidence of intrarenal viral replication by light microscopy and/or immunohistochemistry	N/A
European Society of Clinical Microbiology and Infectious Diseases (ESCMID)	Compatible cytopathic changes in renal tubular cells and demonstration of BKPyV replication by IHC or ISH	Plasma BKPyV loads >10,000 GEq/mL in at least one measurement
Basel Working Group	Intranuclear inclusion bodies, often accompanied by epithelial cell necrosis and tubular injury, confirmed by IHC, ISH, or electron microscopic identification of virions of compatible morphology	Plasma BKPyV load ≥10,000 copies/ml in at least one measurement or VP1 mRNA load ≥6.5 x 10^5 copies/ng total RNA for 3 weeks

Current clinical guidelines

- Variation in use of probable or presumed definitions of BKPyVAN based on viral load
  - Use DNAemia as a surrogate marker, but no measures of allograft dysfunction or histopathology
  - Lack of standardization in BKPyV viral load diagnostics
- Furthermore, there exist variation in definitions of proven disease

Prior to discussion of putative surrogate markers for BKPyVAN, it is essential to establish consensus criteria of BKPyVAN specific to clinical trials and potentially acceptable from regulatory standpoint

Consensus guidelines

- Goal: establish consensus criteria for endpoints in clinical trials that may be acceptable from a regulatory standpoint
- Multidisciplinary:
  - Infectious Diseases
  - Transplant nephrology
  - Renal pathology
  - Molecular diagnostics
  - Regulatory expertise
- Based on critical review of literature and refined over 6 months

JOURNAL ARTICLE

Consensus Definitions of BK Polyomavirus Nephropathy in Renal Transplant Recipients for Clinical Trials

Get access >

Hannah Imlay ✉, Paul Baum, Daniel C Brennan, Kimberly E Hanson, Michael R Hodges, Aimee C Hodowanec, Takashi E Komatsu, Per Ljungman, Veronica Miller, Yoichiro Natori, Volker Nickeleit, Jules O'Rear, Andreas Pikis, Parmjeet S Randhawa, Deirdre Sawinski, Harsharan K Singh, Gabriel Westman, Ajit P Limaye BK Disease Definitions Working Group of the Transplantation Associated Virus Infection Forum With the Forum for Collaborative Research

Clinical Infectious Diseases, Volume 75, Issue 7, 1 October 2022, Pages 1210–1216, https://doi.org/10.1093/cid/ciac071

Published: 01 February 2022 **Article history** ▾

1. Consensus definitions of measures of BKPyV infection
2. Consensus definitions of BKPyVAN
    1. Proven BKPyVAN
    2. Presumed BKPyVAN

Proven BKPyVAN

Demonstration of active BKPyV replication within renal tissue by at least 1 of the following methods:
1. Immunohistochemistry (IHC) staining reaction for SV40-T antigen **OR** in situ hybridization (ISH)
AND
2. Demonstration of BKPyV DNAemia using a previously well-validated assay - avoids misattribution of JCPyV as cause of nephropathy

Optimal allograft biopsy

- Goal: optimize sensitivity
  - At least 2 separate cores should be obtained
  - Biopsy specimen should contain medulla
  - Biopsy specimen should meet Banff criteria for adequacy (consist of 10 glomeruli and 2 arteries)
  - Biopsy specimen should have immunohistochemical or in situ hybridization staining results available

Probable BKPyVAN

A diagnosis of probable BKPyVAN may be established if **all** of the following criteria are met:
1. Allograft biopsy is either not performed or provides a suboptimal specimen
2. Evidence of renal allograft dysfunction (≥20% rise in serum creatinine from baseline)
3. No likely alternative process to explain renal allograft dysfunction
4. **Significant** BKPyV DNAemia in plasma on repeated measurement
Patients with an adequate-quality biopsy without evidence of BKPyVAN should be excluded from consideration for a diagnosis of probable BKPyVAN since the anticipated sensitivity of a renal allograft biopsy in these circumstances would be very high

Probable BKPyVAN

- Several criteria in addition to BKPyV DNAemia in order to increase specificity of diagnosis of BKPyVAN
- What is significant BKPyV replication in plasma?
  - Impaired DNA load standardization across different assays
  - ”Significant” replication is assay dependent
  - Assay in use should be validated against renal allograft biopsies
- BKPyV DNAemia >4 $\log_{10}$ correlated with biopsy-proven BKPyVAN from one assay

Summary

- Consensus criteria established for the design and performance of clinical trials
  - Proven and presumed definitions of BKPyVAN
- Future questions
  - Is BKPyV DNAemia (or other measures of BKPyV replication) an appropriate surrogate for BKPyVAN?
  - What is high-level BKPyV replication?

Questions?

Determination of a plasma viral load threshold for prediction of biopsy-confirmed BK Polyomavirus nephropathy using a standardized BKPyV assay

Hannah Imlay, MD MS

Ajit Limaye, MD

What is significant BKPyV DNAemia?

- BKPyV DNAemia >4 $\log_{10}$ noted to be correlated with biopsy-proven BKPyVAN
- Inter-assay variability limits extrapolation of an absolute cut-off across assays
- FDA cleared BKPyV assay (cobas BKV) for plasma and urine
- Goal: establish a plasma DNA load threshold for biopsy-confirmed BKPyVAN using a commercially available assay
  - Prospectively (200) and retrospectively (30) collected matched plasma and biopsy samples of “for cause” allograft biopsies
  - Anticipate 50 BKPyVAN and 180 non-BKPyVAN samples
  - Establish optimal threshold, sensitivity, and specificity

https://diagnostics.roche.com/us/en/news-listing/2020/roche-receives-fda-clearance-for-bk-virus-quantitative-test-on-c.html

Study design

- Multicenter (~10 centers)
- Prospective and retrospective approaches to collecting matched plasma-biopsy samples
  - Retrospective (n=30): matched plasma-biopsy samples from patients with proven BKPyVAN
  - Prospective (n=20 BKPyVAN, 180 non-BKPyVAN): matched plasma-biopsy samples collected from patients with BKPyV DNAemia undergoing for-cause allograft biopsy

https://diagnostics.roche.com/us/en/news-listing/2020/roche-receives-fda-clearance-for-bk-virus-quantitative-test-on-c.html

Study procedures

- Plasma samples collected at the time of allograft biopsy will be sent to a coordinating site, then batch shipped to central laboratory for assessment of BKPyV load and genotype
- Allograft biopsy samples diagnostic of BKPyVAN will be sent to coordinating site and then shipped for adjudicated pathology review and grading based on Banff histologic class
- Clinical data collected

Objectives

1. Assess the relationship between plasma BKPyV load and allograft biopsy diagnosis and grading of BKPyVAN
2. Explore potential differences in BKPyV geno/sero-type plasma DNA load and BKPyVAN
3. Describe the proportion of “for cause” biopsies that meet Banff criteria for adequacy
4. As funding allows:
    1. Assess short-term biologic variability using serial plasma samples
    2. Assess the relationship of urinary Haufen, plasma BKPyV load, and diagnosis of BKPyVAN

Statistical plan

- Receiver operator curves (ROC) generated using matched plasma-biopsy samples to determine an optimal BKPyV plasma load that optimizes sensitivity and specificity
  - Assess positive and negative predictive value among prospectively-obtained samples
- Machine learning approaches pursued to build a predictive classification model
  - Associated metrics of performance: cross validation and bootstrap

Study deliverables

- Identification of plasma BKPyV threshold with optimal sensitivity and specificity for tissue proven BKPyVAN using a widely available, standardized assay in kidney transplant recipients
- Systematically and rigorously defined relationship between allograft viral load and plasma viral load
- Creation of unique and clinically characterized collection of plasma samples which could be use for assay or biomarker development

Questions?