Viral Infections after Transplantation

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Pediatric Transplantation Teaching Course, Moscow 2016
OVERVIEW

- Timeline of post-transplant infections
- Selected infectious agents:
  - Cytomegalovirus (CMV)
  - Epstein-Barr virus (EBV)
  - Polyomavirus (BKV, JCV)
Timeline of Post-Transplant Infections

Donor-derived

Nosocomial Technical Donor/Recipient

Activation of Latent Infections, Relapsed, Residual, Opportunistic Infections

Community-Acquired

Transplantation

Dynamic Assessment of Infection Risk

< 4 Weeks

Months 1 - 6

> 6 Months

Resistant Species:
- MRSA, VRE, Candida
- Aspiration, Line/Wound Infection, Anastomotic Leaks/Ischemia
- Clostridium diff. Colitis

Donor-Derived (uncommon):
- HSV, LCMV, Rabies, West Nile Virus

Recipient:
- Aspergillus, Pseudomonas

With Prophylaxis:
- Polyomavirus (BKV)
- Clostridium diff. Colitis
- Adenovirus, Influenza, HCV
- Cryptococcus neoform.
- M. tuberculosis

Anastomotic Compl.

Without Prophylaxis (add.):
- Pneumocystis (PcP)
- HSV, VZV, CMV, EBV, HHV-6, HHV-8, HBV
- Listeria, Nocardia, Toxoplasma etc.

Community-Acq. Pneumonia

Urinary Tract Infection
- Aspergillus, Atypical Moulds
- Nocardia, Rhodococcus

Late Viral Infections:
- CMV (Colitis, Retinitis)
- Hepatitis (HBV, HCV)
- HSV Encephalitis
- SARS, West Nile Virus
- Polyomavirus (JCV)

Associated Malignancy:
- PTLD, Kaposi Sarcoma

Am J Transplant 2009, 9(S4): 3; Am J Transplant 2013, 13(S4): 3
Cytomegalovirus (CMV)
Pediatric patients bear a higher risk of primary CMV infection than adults.

<table>
<thead>
<tr>
<th>CMV-Serostatus</th>
<th>Pediatric Patients</th>
<th>Adult Patients²</th>
</tr>
</thead>
<tbody>
<tr>
<td>D+/R-</td>
<td>29.2%</td>
<td>18.2%</td>
</tr>
<tr>
<td>D+/R+</td>
<td>25.9%</td>
<td>39.8%</td>
</tr>
<tr>
<td>D-/R+</td>
<td>9.3%</td>
<td>23.2%</td>
</tr>
<tr>
<td>D-/R-</td>
<td>35.6%</td>
<td>18.8%</td>
</tr>
</tbody>
</table>

¹Höcker et al., Transplantation 2015
²Am J Transplant 2014; 14 Suppl 1: 11
Definition of CMV Infection

**Infection**
Presence of CMV replication regardless of symptoms (viremia (defined as pos. NAT and/or pos. pp65Ag), pos. culture and/or histopathological evidence)

**Disease**
Presence of CMV infection accompanied by clinical symptoms

**Syndrome**
CMV replication plus one or more of the following criteria:
- Fever
- Malaise
- Leukopenia
- Thrombocytopenia

**Tissue-Invasive Disease**
CMV replication plus one or more of the following criteria:
- Gastrointestinal disease
- Pneumonitis
- Hepatitis
- CNS disease
- Retinitis
- Other (nephritis, cystitis, myocarditis, pancreatitis, etc.)
Invasive CMV Disease
Clinical Manifestation of CMV Pneumonitis

Bilateral Interstitial Infiltrates

Ground-Glass Opacity
Invasive CMV Disease
Clinical Manifestation of CMV Colitis

„Burning flame"
Invasive CMV Disease
Histopathology

CMV Hepatitis

CMV Nephritis
Prior Kidney Transplantation

- CMV serology (IgG) in donor and recipient
  - Donor < 12 months and CMV IgG pos. → “CMV pos.”
  - Recipient < 12 months and CMV IgG pos. → “CMV neg.” (maternal antibodies)

Post-Transplant

- CMV quantitative NAT (QNAT) in plasma or whole-blood
  (preferred method of diagnosis and monitoring response to therapy; calibration of assay according to WHO standard; no change of specimen type)

- CMV pp65Ag is an acceptable alternative.
  (cave: sample processing within 6 - 8 hrs; diagnostically less conclusive in case of leukocytopenia)

- Histology/immunohistochemistry for diagnosis of tissue-invasive disease

- CMV culture and QNAT of tissue specimens only in case of gastrointestinal disease and pneumonitis (BAL)

An ounce of prevention is worth a pound of cure.

B. Franklin
Prevention Strategies

Vaccination

Antiviral Prophylaxis

Hybrid Approach

Preemptive Therapy

Adaptive Cell Therapy

Adaptation of Immunosuppressive Medication
Cytomegalovirus in Solid Organ Transplantation

R. R. Razonable\textsuperscript{a, *}, A. Humar\textsuperscript{b} and the AST
Infectious Diseases Community of Practice

Updated International Consensus Guidelines
on the Management of Cytomegalovirus
in Solid-Organ Transplantation

Camille N. Kotton\textsuperscript{1,8} Deepali Kumar\textsuperscript{2} Angela M. Caliendo\textsuperscript{3} Anders Åsberg\textsuperscript{4}
Sunwen Chou\textsuperscript{5} Lara Danziger-Isakov\textsuperscript{6} and Atul Humar\textsuperscript{7}
on behalf of The Transplantation Society International CMV Consensus Group

Transplantation • Volume 96, Number 4, August 27, 2013
# Chemoprophylaxis

<table>
<thead>
<tr>
<th>Serostatus</th>
<th>Risk Level</th>
<th>Recommended</th>
<th>Alternate</th>
</tr>
</thead>
<tbody>
<tr>
<td>D+/R-</td>
<td>Intermediate to high</td>
<td>3 - 6 mths of valganciclovir (or ganciclovir i.v.) as recommended in adults&lt;sup&gt;A&lt;/sup&gt; OR 2 - 4 wks of valganciclovir (or ganciclovir i.v.) with sequential monitoring</td>
<td></td>
</tr>
<tr>
<td>R+</td>
<td>Low</td>
<td>2 - 4 wks of valganciclovir (or ganciclovir i.v.) with sequential monitoring</td>
<td>3 - 6 mths of valganciclovir (or ganciclovir i.v.) as recommended in adults&lt;sup&gt;A&lt;/sup&gt;</td>
</tr>
<tr>
<td>D-/R-</td>
<td>Lowest</td>
<td>Monitoring for clinical symptoms</td>
<td>Preemptive monitoring</td>
</tr>
</tbody>
</table>

<sup>A</sup>T cell-depleting induction is associated with increased risk of CMV replication and disease; consider prolonged prophylaxis or more intensive monitoring.

*Transplantation* 2013; 96: 333
Valganciclovir Dosage for CMV Prophylaxis

FDA Issues New Dosing Recommendations For Valganciclovir:
… children with low body weight, low body surface area, and very low serum creatinine could have a high calculated creatinine clearance requiring a dose of the antiviral approaching the maximum 900-mg dose used in adults…
…To minimize the potential for overdose, the FDA has set a maximum value for the calculated creatinine clearance of 150 ml/min⋅1.73 m²…
… formula yields a dose higher than 900 mg, the 900-mg dose should be used…

MedPage Today, September 15, 2010

Dose (mg/d) = 7 x BSA (m²) x eGFR* (ml/min⋅1.73 m²)

- *Schwartz formula: eGFR = height (cm)/serum creatinine (mg/dl) x 0.413
- Max. eGFR = 150 ml/min⋅1.73 m²
- Max. daily dose 900 mg

Am J Transplant 2009; 9: 636
Association between VGCV Prophylaxis and CMV Replication in CMV High-risk (D+/R-) Patients

Höcker B et al., Transplantation 2015
Direct and Indirect Effects of CMV

Infection

Graft rejection

Anti-lymphocyte antibodies

Inflammation (cytokines, growth factors, intracellular messengers, NF-κB)

Latent CMV infection

Active CMV infection (viremia and invasion)

CMV syndrome

Tissue-invasive disease

Flu-like and mononucleosis-like syndromes

Nephritis, hepatitis, carditis, pneumonitis, pancreatitis, colitis, retinitis

Direct effects

Indirect effects

Cellular effects: antigen and cytokine expression

Allograft injury

Acute

Atherosclerosis, bronchiolitis obliterans, vanishing bile-duct syndrome

Chronic

Allograft rejection

Acute

EBV-associated PTLD

Systemic immune suppression

Opportunistic infection

Clin Transplant 2007; 21: 149
CMV-Associated Pathology of Kidney Allograft

- Intrgraft CMV protein expression is associated with reduced renal allograft survival.  
  \cite{Clin Infect Dis 2011}

- CMV increases tubular apoptosis through the TNF-α–TNF-R1 pathway in a rat model of chronic renal allograft rejection.  
  \cite{Transpl Immunol 2008}

- Persistent CMV infection is associated with increased expression of TGF-β₁, PDGF-AA and ICAM-1 and arterial intimal thickening in kidney allografts.  
  \cite{NDT 2005; Transpl Immunol 2006}

- CMV induces TGF-β₁ activation in renal tubular epithelial cells after epithelial-to-mesenchymal transition.  
  \cite{PLoS Path 2010}
Reduced Graft Function in Pediatric RTx Patients with CMV Replication

Independent risk factors for eGFR loss (multivariate analysis):
- CMV replication ($P < 0.05$)
- Acute rejection ($P < 0.05$)
- Recipient’s age ($P < 0.001$)

Höcker B et al., Transplantation 2015
### Hematological Data

<table>
<thead>
<tr>
<th>Hematological data</th>
<th>Prophylaxis group (n = 99)</th>
<th>Control group (n = 143)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anemia [Hb &lt; 8 g/dl], n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Up to 100 days post-transplant</td>
<td>18/99 (18%)</td>
<td>12/143 (9%)</td>
<td>0.023</td>
</tr>
<tr>
<td>During 1st year post-transplant</td>
<td>24/99 (24%)</td>
<td>26/143 (18%)</td>
<td>0.252</td>
</tr>
<tr>
<td><strong>Leukopenia [leukocytes &lt; 3500/µl], n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Up to 100 days post-transplant</td>
<td>22/99 (22%)</td>
<td>12/143 (9%)</td>
<td>0.002</td>
</tr>
<tr>
<td>During 1st year post-transplant</td>
<td>34/99 (34%)</td>
<td>27/143 (19%)</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Neutropenia [neutrophils &lt; 1300/µl], n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Up to 100 days post-transplant</td>
<td>15/64 (23%)</td>
<td>10/103 (10%)</td>
<td>0.016</td>
</tr>
<tr>
<td>During 1st year post-transplant</td>
<td>19/58 (33%)</td>
<td>17/84 (20%)</td>
<td>0.092</td>
</tr>
<tr>
<td><strong>Agranulocytosis [granulocytes &lt; 500/µl], n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Up to 100 days post-transplant</td>
<td>8/64 (13%)*</td>
<td>1/103 (1%)</td>
<td>0.001</td>
</tr>
<tr>
<td>During 1st year post-transplant</td>
<td>11/58 (19%)</td>
<td>2/84 (2%)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Thrombocytopenia [thrombocytes &lt; 100/µl], n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Up to 100 days post-transplant</td>
<td>4/99 (4%)</td>
<td>8/143 (6%)</td>
<td>0.584</td>
</tr>
<tr>
<td>During 1st year post-transplant</td>
<td>6/99 (6%)</td>
<td>8/143 (6%)</td>
<td>0.879</td>
</tr>
</tbody>
</table>

*3 of 8 (38%) patients received overdosing of VGCV by 46-64% prior to agranulocytosis.
Therapy

Asymptomatic CMV Infection
- Ganciclovir i.v. (5 mg/kg b.i.d.) in children aged < 5 years
- Valganciclovir p.o. (2-fold prophylactic dosage) in older patients
- Reduction of immunosuppression where indicated

CMV Disease
- Ganciclovir i.v. (5 mg/kg b.i.d.) in children aged < 12 years
- Valganciclovir p.o. (2-fold prophylactic dosage) in older patients
- CMV Ig i.v. (in addition to above-mentioned antiviral agents) in patients with severe CMV disease (i.e., pneumonitis, enteritis) and in those with hypogammaglobulinemia during CMV infection or disease

Epstein-Barr-Virus (EBV)
## Epstein-Barr Virus (EBV) Infection and Post-Transplant Lymphoproliferative Disease (PTLD)

<table>
<thead>
<tr>
<th>Location</th>
<th>Primary Infection</th>
<th>Persistent Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saliva</td>
<td>EBV</td>
<td>EBV</td>
</tr>
<tr>
<td>Oro-pharynx</td>
<td>Epithelium</td>
<td>Epithelium</td>
</tr>
<tr>
<td>Lymphatic tissue and circulating blood</td>
<td>Quiescent B cell</td>
<td>Latently infected, quiescent B cell</td>
</tr>
<tr>
<td></td>
<td>EBV-infected B cell blast</td>
<td>Reactivated EBV-infected B cell</td>
</tr>
<tr>
<td></td>
<td>LMP-1</td>
<td>LMP-1</td>
</tr>
<tr>
<td></td>
<td>LMP-2</td>
<td>LMP-2</td>
</tr>
<tr>
<td></td>
<td>EBNA-1</td>
<td>EBNA-1</td>
</tr>
<tr>
<td></td>
<td>Cytotoxic T cell</td>
<td>Cytotoxic T cell</td>
</tr>
<tr>
<td></td>
<td>Natural killer cell</td>
<td>Natural killer cell</td>
</tr>
</tbody>
</table>

- Mostly mild cytopathic properties
- But ability to immortalize B cells
- Under immunosuppression risk of malignant B cell transformation
- 90% of PTLDs in pediatric patients induced by EBV

Modified according to *N Engl J Med* 2000; 343: 481
Risk Factors For PTLD

Early PTLD (≤12 months post-transplant)
- Primary EBV infection
- OKT3 and polyclonal antilymphocyte antibodies
- Young recipient age (i.e., infants and young children)
- CMV mismatch or CMV disease

Late PTLD (>12 months post-transplant)
- Duration of immunosuppression
- Older recipient age (i.e., adults)
EBV-Seronegativity at RTx as Risk Factor for the Development of Non-Hodgkin Lymphoma (NHL)

Recipient EBV Serostatus at RTx

Incidence of NHL

Rec EBV-

Incidence of NHL

Rec EBV+

Cumulative Incidence (per 100,000)

Years

EBV- n= 2,711

EBV+ n=17,922
Spectrum of EBV Infection and Disease

- Asymptomatic EBV infection
- Unspecific flu-like symptoms
- Infectious mononucleosis

### PTLD Categories (WHO Classification)

<table>
<thead>
<tr>
<th>I. Early lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Plasmacytic hyperplasia</td>
</tr>
<tr>
<td>- Infectious mononucleosis-like lesion</td>
</tr>
<tr>
<td>II. Polymorphic PTLD</td>
</tr>
<tr>
<td>III. Monomorphic PTLD (B-, T- or NK-cell type)</td>
</tr>
<tr>
<td>IV. Classical Hodgkin lymphoma-type PTLD</td>
</tr>
</tbody>
</table>
Diagnostics

Prior Kidney Transplantation

- EBV serology (IgG) in donor and recipient for risk assessment

Post-Transplant

- EBV viral load
  - Lack of standardization in terms of specimen (whole-blood, lymphocyte, plasma), cut-off value (WHO international standard has yet to be validated.)
  - Monitoring schedule?
  - Poor positive predictive value for PTLD (28 – 65%)
- EBV-specific T cell response
  - Assays are complex, costly and difficult to implement in routine diagnostic laboratory.
EBV load screening and monitoring

**Viral load**

- **Mononucleosis**
- **PTLD**
- **Lymphoma**

**Symptoms**

- Ganciclovir
- anti-CD20
- CHOP

**Detection**

- Lower IS

**Transplantation**

**Time**
EBV Viral Load and EBV-Associated Clinical Symptoms

Clin Infect Dis 2013; 56: 84
Antiviral Prophylaxis

- EBV-naïve (R-) recipients of EBV-positive kidney allograft (D+) carry a high risk of primary EBV infection.  
  *Am J Hematol 2011; 86: 206*

- Subclinical EBV infection is accompanied by chronic allograft dysfunction.  
  *J Am Soc Nephrol 2010; 21: 1579*

- Cumulative incidence of NHL is significantly increased (p<0.001) in EBV-negative kidney allograft recipients.  
  *Transplantation 2009; 88: 962*

- CMV Ig is associated with significantly lower (p<0.02) NHL risk.  
  *Lancet Oncol 2007; 8: 212*

- Antiviral chemoprophylaxis (ganciclovir/acyclovir) is accompanied by an up to 83% reduction of the PTLD risk.  
  *Am J Transplant 2005; 5: 2894*

Effect of antiviral prophylaxis with (val-)ganciclovir on the incidence and morbidity of primary EBV infection in high-risk (D+/R-) patients?
(Val-)Ganciclovir prophylaxis reduces Epstein-Barr virus primary infection in pediatric renal transplantation

Britta Höcker,1 Stephan Böhm,2,3 Helmut Fickenscher,2,4 Uta Küsters,2 Paul Schnitzler,2 Martin Pohl,5 Ulrike John,6 Markus J. Kemper,7 Henry Fehrenbach,8 Marianne Wigger,9 Martin Holder,10 Monika Schröder,11 Reinhard Feneberg,1 Sabine Köpf-Shakib1 and Burkhard Tönshoff1

1 University Children’s Hospital, Heidelberg, Germany
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3 Department of Gastroenterology, University Hospital Leipzig, Leipzig, Germany
4 Institute for Infection Medicine, University of Kiel, Kiel, Germany
5 University Children’s Hospital, Freiburg, Germany
6 University Children’s Hospital, Jena, Germany
7 University Children’s Hospital, Hamburg, Germany
8 Children’s Hospital, Memmingen, Germany
9 University Children’s Hospital, Rostock, Germany
10 Olga Children’s Hospital, Stuttgart, Germany
11 Clementine Children’s Hospital, Frankfurt, Germany
Effect of Antiviral Chemoprophylaxis with (Val-)Ganciclovir on the Incidence of Primary EBV Infection in High-Risk (D+/R-) Patients

Transpl Int 2012; 25: 723
Polyomavirus (BKV)
Primary Infection
- Occurs during first decade (seropositivity ~90%).
- Unspecific flu-like symptoms
- Transmission via respiratory tract

Persistent / Latent Infection
- Kidney, urothelial cells
- CNS? Leukocytes? Gastrointestinal tract?

Reactivation

Immunological Competence
- Reactivation ~ 10% → viruria <10^5 cp/ml

Immunosuppression
- RTx: reactivation of BKV in donor urothelial cells
- Shedding of “decoy cells”
- High-level viruria in 30 - 50% of patients after RTx → viruria >10^7 cp/ml
- 30% of patients with high-level viruria develop BKV viremia
- Premature graft failure in 1 - 15% due to BKV
Diagnostics

Urine

- **Cytology** („decoy cells“, not pathognomonic: CMV, adenovirus)

- **Viral Load** (BKV DNA load $>10^7$ cp/ml; BKV VP1 mRNA load $>10^{6.5}$/ng RNA)
  
  **Advantages**: high negative predictive value for polyomavirus-associated nephropathy (PyVAN), window period of 6 – 12 wks before viremia and nephropathy

  **Disadvantage**: low positive predictive value for PyVAN

- **PyV Aggregates** („Haufen“)
  
  **Advantage**: high (>90%) positive and negative predictive value for PyVAN

  **Disadvantage**: expertise in EM of PyV aggregates required

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Blood

Viral Load (BKV DNA load $>10^4$ cp/ml)

Positive predictive value (PPV) for PyVAN 30 – 50%, window period of 2 – 6 wks before PyVAN, BKV DNA load $>10^4$ cp/ml → “presumed” PyVAN, BKV DNA load $>10^6$ cp/ml → “proven” PyVAN (PPV 90%)

Graft Biopsy

Immunohistochemistry (T-Ag SV40, VP1)

≥2 cylinders, also medullary tissue (sampling error in 10 - 30%)

<table>
<thead>
<tr>
<th>Histology</th>
<th>Description</th>
<th>Extent of Bx Core</th>
<th>Risk of Graft Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PyVAN A</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Viral cytopathic changes</td>
<td>Mild</td>
<td>≤25%</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>- Interstitial inflammation</td>
<td>Minimal</td>
<td>≤10%</td>
<td></td>
</tr>
<tr>
<td>- Tubular atrophy</td>
<td>Minimal</td>
<td>≤10%</td>
<td></td>
</tr>
<tr>
<td>- Interstitial fibrosis</td>
<td>Minimal</td>
<td>≤10%</td>
<td></td>
</tr>
</tbody>
</table>

| **PyVAN B** | | | |
| - Viral cytopathic changes | Variable | | 50% |
| - Interstitial inflammation | Significant | 11 - >50% | |
| - Tubular atrophy | Moderate | 11 - >50% | |
| - Interstitial fibrosis | Moderate | <50% | |
| **PyVAN B1** | - Interstitial inflammation | Moderate | 25% |
| **PyVAN B2** | - Interstitial inflammation | Significant | 50% |
| **PyVAN B3** | - Interstitial inflammation | Extensive | 75% |

| **PyVAN C** | | | |
| - Viral cytopathic changes | Variable | Variable | Am J Transplant 2013; 13: 179 |
| - Interstitial inflammation | Variable | Variable | |

<80%
Therapy of PyVAN: Reduction of Immunosuppression

**Strategy 1**
1. CNI (TAC, CSA) dose reduction by 25 - 50%
2. Reduction of antimetabolite (MMF, AZA) dosage by 50% or discontinuation

**Strategy 2**
1. Reduction of antimetabolite (MMF, AZA) dosage by 50%
2. CNI (TAC, CSA) dose reduction by 25 - 50%
3. Discontinuation of antimetabolite

<table>
<thead>
<tr>
<th>Immunosuppressant</th>
<th>Pre-Dose Level / Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAC</td>
<td>&lt;6 ng/ml (target 3 ng/ml)</td>
</tr>
<tr>
<td>CSA</td>
<td>&lt;150 ng/ml (target 100 ng/ml)</td>
</tr>
<tr>
<td>SRL</td>
<td>&lt;6 ng/ml</td>
</tr>
<tr>
<td>MMF</td>
<td>&lt;1000 mg/d (corresp. &lt;600 mg/m²·d)</td>
</tr>
<tr>
<td>Prednisone</td>
<td>&lt;10 mg/d (corresp. &lt;5.8 mg/m²·d)</td>
</tr>
</tbody>
</table>

Conversion of immunosuppressive regimen

*Am J Transplant 2013; 13: 179*
Adjunctive Therapy of PyVAN

Cidofovir (Vistide®)
- 0.25 - 1 mg/kg i.v. at 1- to 3-week intervals
- Cave: nephrotoxicity, anterior uveitis (12 - 35%)

Leflunomide (Arava®)
- Substitute for MMF
- Loading dose 100 mg/d for 5 days, maintenance dose 40 mg/d
- Cave: hepatitis, hemolysis, thrombotic microangiopathy, bone marrow suppression, fungal pneumonia

IVIG
- 0.2 – 2 g/kg i.v. in conjunction with reduced immunosuppression

Fluoroquinolones?
Screening
- Every 3 mths during first 2 yrs post-transplant or
- If allograft dysfunction
- If allograft biopsy

BKV viruria

Positive

BKV viremia

Positive

Allograft biopsy

Positive "definitive PyVAN"

Reduce immunosuppression

BKV viremia

Negative "resolved PyVAN"

Negative or not done "presumptive PyVAN"

- Urine cytology (decoy cells) or
- Urine EM (PyV aggregates) or
- Urine BKV load (>10⁷ cp/ml)

- Plasma BKV load >10⁴ cp/ml

Other diagnosis
- Acute rejection?
- Drug toxicity?
- Recurrent disease?

- Staging (PyVAN A, B₁, B₂, B₃, C)

- Reduce CNI, MMF…
- Add cidofovir? Leflunomide? IVIG?

Follow-up
- Serum creatinine weekly
- Plasma BKV load every 1 - 2 wks (clearing 8 - 36 wks)
- Allograft biopsy?
- Raise immunosuppression?
Thank You!