Viral infections after renal transplant: BK and CMV
Infection in Solid-Organ Transplant Recipients

Jay A. Fishman, M.D.

Increasingly potent immunosuppressive agents have dramatically reduced the incidence of rejection of transplanted organs while increasing patients’ susceptibility to opportunistic infections and cancer. At the same time, patterns of opportunistic infections after transplantation have been altered by routine antimicrobial prophylaxis for Pneumocystis carinii (also called P. jirovecii) and cytomegalovirus. These patterns have also been altered by the emergence of new clinical syndromes (e.g., polyomavirus type BK nephropathy) and by infections due to organisms with antimicrobial resistance. New quantitative molecular and antigen-based microbiologic assays detect previously unrecognized transplantation-associated pathogens such as lymphocytic choriomeningitis virus. These assays are used in the management of common infections such as those due to cytomegalovirus and Epstein–Barr virus (EBV). In this article, I review general concepts in the management of transplantation-associated infections and discuss recent advances and challenges.
The NEW ENGLAND JOURNAL of MEDICINE

Donor-Derived Infection

- Nosocomial, technical (donor or recipient)
- Activation of latent infection (relapsed, residual, opportunistic)
- Community-acquired

Transplantation

Recipient-Derived Infection

- <1 Month
  - Infection with antimicrobial-resistant species:
    - MRSA
    - VRE
    - Candida species (non-albicans)
  - Aspiration
  - Catheter infection
  - Wound infection
  - Anastomotic leaks and ischemia
  - Clostridium difficile colitis
  - Donor-derived infection (uncommon):
    - HSV, LCMV, rhabdovirus (rabies), West Nile virus, HIV, Trypanosoma cruzi
  - Recipient-derived infection (colonization):
    - Aspergillus, pseudomonas

- 1–6 Months
  - With PCP and antiviral (CMV, HBV) prophylaxis:
    - Polyomavirus BK infection, nephropathy
    - C. difficile colitis
    - HCV infection
    - Adenovirus infection, influenza
    - Cryptococcus neoformans infection
    - Mycobacterium tuberculosis infection
    - Anastomotic complications
  - Without prophylaxis:
    - Pneumocystis
    - Infection with herpesviruses (HSV, VZV, CMV, EBV)
    - HBV infection
    - Infection with listeria, nocardia, toxoplasma, strongyloides, leishmania, T. cruzi

- >6 Months
  - Community-acquired pneumonia, urinary tract infection
  - Infection with aspergillus, atypical molds, mucor species
  - Infection with nocardia, rhodococcus species
  - Late viral infections:
    - CMV infection (colitis and retinitis)
    - Hepatitis (HBV, HCV)
    - HSV encephalitis
    - Community-acquired (SARS, West Nile virus infection)
    - JC polyomavirus infection (PML)
    - Skin cancer, lymphoma (PTLD)

Common Infections in Solid-Organ Transplant Recipients

Dynamic assessment of risk of infection
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Interactions Between Anti-Infective Agents and Immunosuppressants in Solid Organ Transplantation
BK virus
BK virus

What does BK stand for?
The BK virus was first isolated in 1971 from the urine of a renal transplant patient, initials ....
The BK virus was first isolated in 1971 from the urine of a renal transplant patient, initials B.K.

New human papovavirus (B.K.) isolated from urine after renal transplantation.
Polyoma viruses

- Small double-stranded DNA viruses
- Infect a variety of animals
- High worldwide prevalence
Human polyomaviruses

- **BK virus**: isolated in 1971 from the urine of a renal allograft recipient with ureteric obstruction.
- **JC virus** (also named for the patient’s initials): cultivated in 1971 from the brain of a patient with progressive multifocal leukoencephalopathy in the context of Hodgkin's disease.
- **KI virus** (“Karolinska Institutet”): identified 2007 using large-scale molecular virus screening method to identify unrecognized human pathogens.
- **WU virus** (“Washington University”): identified 2007 from respiratory secretions of patients with URI symptoms.
- **MCV virus**: found in Merkel cell carcinomas in 2008.
BK virus

• Primary infection with BKV occurs in the first decade of life as evidenced by seroprevalence to 90% or more
• Mode of transmission uncertain, but likely occurs via the respiratory or oral route
• Asymptomatic or mild URI in immunocompetent hosts
BK virus

• BKV colonizes the renourinary tract as the principle site of latent infection
• In healthy BKV seroprevalent immunocompetent individuals, reactivation and asymptomatic urinary shedding of BKV is detectable in up to 10%
Clinical manifestations

• BKV linked to 2 major complications in transplant recipients:
  – BKV nephropathy in 1-10% of kidney transplant patients
  – Polyomavirus-associated hemorrhagic cystitis in 5-15% of allogeneic hematopoietic stem cell transplant patients
Clinical manifestations

• In individuals with impaired immune functions, such as after organ transplant, there can be asymptomatic high level urinary BKV replication, appearance of “decoy cells” in urine cytology, and virus particles detectable by electron microscopy.
Urine cytology specimen demonstrating the findings associated with polyomavirus-associated nephropathy

(A) Urine cytology specimen depicting scattered "decoy cells" with ground-glass, homogeneous nuclear inclusions (Papanicolaou, × 1000).
(B) Urine cytology specimen depicting vesicular variant decoy cells with enlarged nuclei with clumped, irregular chromatin (Papanicolaou, × 1000).
(C) Urine cytology specimen with tubular casts containing numerous compacted decoy cells indicative of polyomavirus-associated nephropathy (Papanicolaou, × 400). UpToDate
Urine microscopy showing “decoy” cells

Urine cytology sediment demonstrates three "decoy" cells, characterized by large viral nuclear inclusions that replace the normal chromatin (Papanicolaou stain). The nuclear inclusion is formed by dark, smudged material representing thousands of newly formed virions (V). Electron microscopy (insert) shows the contrast between the inclusion (V) and the darker surrounding chromatin.

UpToDate
• In kidney transplant recipients, those with high-level BKV viruria/decoy cells can develop BKV viremia
• Viremia can progress to BKV nephropathy
Type and prevalence of BK virus (BKV) infections in kidney transplant recipients

- Viruria: 30-40%
- Decoy cells: 20-30%
- Viremia: 10-20%
- Nephropathy: 0-10%
- Graft loss: 0-5%

*Rare cases of nephropathy without viremia or viremia without viruria may occur.

CJASN
BKPyV events following renal transplantation.

J Bras Nefrol 2014;36(4):529-534
Diagnosis

- Urine cytology
- Urine PCR
- Urine electron microscopy
- Serum PCR
- Kidney transplant biopsy
Diagnosis: Electron Microscopy

A) Free viral particles (\(\sim 45 \text{ nm diameter}\)) shed in the urine.

B) Polyoma Allograft Nephropathy: 3D, cast-like polyomavirus aggregates ('Haufen') in urine are diagnostic of intra-renal disease.

Kidney biopsy revealing several tubular cells with enlarged nuclei with intranuclear inclusions and homogenous ground glass appearance.
Staining for SV40

True or False

BKV nephropathy is a sign of over-immunosuppression
Immune Suppression

Inadequate

Rejection

Allograft dysfunction

Tubulointerstitial nephritis

Fibrosis

Excessive

BKV Nephropathy
• Because safe and effective antiviral therapies are lacking, screening for BK replication is key
Screening

- Kidney transplant recipients should be screened for BKV replication to identify patients at increased risk for BKV nephropathy
  - Urine for BKV viruria/decoy cells
  - Plasma for BKV viremia
Screening

• Screening should be performed at least every 3 months during the first 2 years post transplant, and then annually until the 5\textsuperscript{th} year post transplant

• Using this strategy, at least 80-90\% of patients at risk can be identified before significant functional impairment occurs
Screening

• Additional screening should occur with unexplained rises in serum creatinine or following treatment for acute rejection
Screening protocol based on plasma BKV DNA PCR (CJASN)
Treatment

• Reducing immunosuppression should be considered for kidney transplant patients with sustained plasma BKV loads
Transplant – Monitoring and Treatment Guideline for BK Polyomavirus in Kidney Transplant Recipients

**Scope:** Physicians, APRNs, Physician Assistants, Pharmacists, Nurses, and other healthcare providers

**Outcome:** To outline appropriate diagnosis, monitoring, and treatment of BK polyomavirus in immunosuppressed patients post-transplant.

**Supportive Data:** Primary infection with the BK polyomavirus (BKV) occurs in 90% of the population in the first decade of life. BKV is the leading cause of polyomavirus-associated nephropathy (PyVAN) in patients post-kidney transplant. PyVAN is preceded by BKV viremia; detection in this stage can lead to clearing of the virus prior to functional damage to the transplanted kidney if treatment is changed appropriately. The diagnosis of PyVAN in the absence of BKV viruria and/or viremia is extremely unlikely. Patients who develop BKV viremia and receive no intervention typically progress to histologically proven PyVAN. The risk of graft loss increases to >90% for patients who develop proven PyVAN.
1. Treatment of BKV should consist of decreasing immunosuppression as outlined below:
   a. Without concurrent acute rejection:
      i. Initiate at least one of the following treatment options

         • Decrease antiproliferative agent by ≥50%
         • Discontinue antiproliferative agent
         • Decrease calcineurin inhibitor by ≥50%

   Recommended drug levels/doses:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Level/Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tacrolimus trough</td>
<td>&lt; 6 ng/mL</td>
</tr>
<tr>
<td>Cyclosporine trough</td>
<td>&lt; 150 ng/mL</td>
</tr>
<tr>
<td>Sirolimus trough</td>
<td>&lt; 6 ng/mL</td>
</tr>
<tr>
<td>Mycophenolate total daily dose</td>
<td>≤ 1000 mg</td>
</tr>
<tr>
<td>Prednisone total daily dose</td>
<td>≤ 5 mg</td>
</tr>
</tbody>
</table>
• In patients with sustained high level plasma BKV loads despite adequately reduced immunosuppression, use of adjunctive antiviral agents may be considered.
Cidofovir

• Originally used for treatment of cytomegalovirus retinitis
• Given IV for BK nephropathy, 1-3 weekly intervals
• Shown to have in vitro activity against BKV
• Side effect is nephrotoxicity
Leflunomide (Arava®)

- Anti-rheumatic drug
- Discontinue mycophenolate
- Loading dose 100mg
  PO daily x 5 days
- Maintenance dose
  20-40 mg daily
- Monthly CBC and LFTs
Fluoroquinolones

- Can inhibit BKV replication
- Modest antiviral effect
- Treatment of well established BKV nephropathy may not be effective
Intravenous immunoglobulin

- 1 gm/kg x 2 doses IV
- Contain high titers of potent BKV neutralizing antibodies
• There are no randomized controlled trials providing evidence that adjunctive use of these agents is superior to timely reduction of immunosuppression
• Retransplantation is not contraindicated if there is a loss of allograft secondary to BKV nephropathy
  – Prior to retransplant, plasma BKV viral load should be undetectable
CMV virus

Cytomegalovirus (CMV)

- Polymerase
- Double Stranded DNA
- Icosohedral Capsid
- Tegument
- Lipid Bi-layer
- Glycoprotein
CMV virus

• Herpes virus (Human Herpes Virus 5)
• Infects the majority of humans
• Seroprevalence ranges from 30-97%
<table>
<thead>
<tr>
<th>Human herpes type</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Herpes simplex-1 (HSV-1)</td>
</tr>
<tr>
<td>2</td>
<td>Herpes simplex-2 (HSV-2)</td>
</tr>
<tr>
<td>3</td>
<td>Varicella Zoster virus (VZV)</td>
</tr>
<tr>
<td>4</td>
<td>Epstein-Barr Virus (EBV)</td>
</tr>
<tr>
<td>5</td>
<td>Cytomegalovirus (CMV)</td>
</tr>
<tr>
<td>6</td>
<td>Human herpes virus-6 (HHV-6)</td>
</tr>
<tr>
<td>7</td>
<td>Human herpes virus-7 (HHV-7)</td>
</tr>
<tr>
<td>8</td>
<td>Human herpes virus-8 (HHV-8)</td>
</tr>
</tbody>
</table>
Worldwide CMV seroprevalence rates in adults

Front. Microbiol., September 2015
Transmission

• **Via body fluids**: CMV has been cultured from multiple sites, including urine, blood, throat, cervix, semen, stool, tears, and breast milk

• **Via organ transplant**
CMV is short for cyto-megalo-virus

CMV is common

Most common virus transmitted from a pregnant woman to her unborn child

1 in 150 children are born with congenital CMV

1 in 3 pregnant women who get CMV will pass the virus to their unborn child

More common than the 29 combined metabolic and endocrine disorders in the recommended US newborn screening panel
CMV

• Primary infection manifests as an asymptomatic or self-limited febrile illness in immunocompetent individuals

• After which, the virus remains latent in most healthy adults
CMV

• CMV is a major cause of morbidity in renal transplant recipients
• Can be preventable

“I’ll have an ounce of prevention.”
CMV

• Without a prevention strategy, CMV disease typically occurs during the first 3 months after solid organ transplant
• This onset has been delayed in patients receiving CMV prophylaxis
Infection vs disease

- **CMV infection**
  - Presence of CMV replication regardless of symptoms (≠ latent CMV)

- **CMV disease**
  - CMV infection accompanied by clinical signs and symptoms
CMV disease

• Fever, malaise
• Leukopenia, thrombocytopenia
• Tissue invasive disease: GI disease, pneumonitis, hepatitis, nephritis, myocarditis, pancreatitis, retinitis etc
Risk assessment

- All transplant donors and recipients are screened for CMV prior to transplant to allow for risk stratification and guide prevention strategies
Figure 2. Serologic Risk Profile for the Development of CMV Disease in Transplant Patients

- **D+** Donor Seropositive
- **R-** Recipient Seronegative
- **D+** Donor Seropositive
- **R+** Recipient Seropositive
- **D-** Donor Seronegative
- **R+** Recipient Seropositive
- **D-** Donor Seronegative
- **R-** Recipient Seronegative

**Risk of CMV Disease**

*Courtesy of Genentech*
Additional risk factors

- Overall state of immunosuppression
  - drug, dose, duration
- Use of lymphocyte depleting agents
- Recipient factors
  - age, comorbidity, leukopenia
Laboratory diagnosis

- Serology (CMV IgG and IgM)
- Antigenemia (pp65 antigen) - immunofluorescence
- Molecular assays (PCR, NAT)
- Histopathology
- Culture
CYTOMEGALOVIRUS
NUCLEAR INCLUSIONS
WITH PERINUCLEAR HALO

cytoplasmic
inclusions

reactive alveolar lining cells
Cytomegalovirus (CMV) pneumonitis in the lung, H&E stain
CMV colitis
Ulcers on endoscopy

Viral Inclusion

Immunostain for CMV

Normal endoscopy

No Viral Inclusions
Prevention of CMV disease

• 2 major strategies
  – Prophylactic therapy
  – Preemptive therapy
Prophylactic therapy

• Administration of antiviral drug to all “at risk” patients for a defined period after transplant, prior to detection of active CMV infection
Preemptive therapy

• Administration of antiviral drug only to asymptomatic patients with evidence of early CMV replication in order to prevent CMV disease

• To be effective, recipients are monitored regularly (usually weekly) using a laboratory assay
Prophylaxis vs Preemptive

• Which strategy to use is resource and center dependent
• Hartford Hospital uses prophylactic strategy
• Prophylaxis is better at preventing active CMV infection
Transplant – Adult CMV Prevention and Treatment for Solid Organ Transplant Guideline

Scope: Physicians, nurse-practitioners, physician-assistants, pharmacists, nurses and other health care providers

Outcome: To provide guidance for CMV prophylaxis and treatment in kidney, liver, heart transplant patients

Supportive Data: Risk of developing CMV disease is largely based on the CMV serostatus of both the donor and recipient. The highest CMV risk is in donor-positive, recipient-negative patients. Other risk factors include overall immunosuppression state, host factors, and use of anti-lymphocyte antibody agents as either induction or rejection therapy. Prophylaxis should be initiated within one week of kidney, liver, or heart transplant. Valganciclovir (Valcyte) doses should be adjusted based on renal function.
Post-Transplant Prophylaxis

Prophylaxis for D+/R- Patients
1. Valganciclovir (Valcyte) 900 mg PO daily for 6 months
2. For all patients receiving antilymphocyte antibody agents (ie. Thymoglobulin) for induction
3. For D-/R- patients who receive extensive transfusions

Prophylaxis for R+
- Valganciclovir (Valcyte) 900 mg PO daily for 3 months
- Patients receiving antilymphocyte antibody agents (ie. Thymoglobulin) for induction will receive 6 months

Prophylaxis for D-R-
- Prophylaxis for other herpes infections (varicella and herpes simplex)
- ValACYclovir (Valtrex) 500 mg PO daily for 3 months
- Use leukodepleted blood products and CMV-seronegative blood
- Patients who receive extensive transfusions should be considered high risk and treated as D+/R- patients (see above)
Adjustment for renal dysfunction for prophylaxis or maintenance dosing (post-induction treatment):

<table>
<thead>
<tr>
<th>Estimated CrCl (mL/min)</th>
<th>Dose of Valganciclovir (Valcyte)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50</td>
<td>900 mg PO daily</td>
</tr>
<tr>
<td>30-49</td>
<td>450 mg PO daily</td>
</tr>
<tr>
<td>10-29</td>
<td>450 mg PO q 48 h</td>
</tr>
<tr>
<td>&lt;10 or on dialysis</td>
<td>450 mg PO twice a week</td>
</tr>
</tbody>
</table>
Drug Therapy for CMV Disease

1. For non-severe CMV disease
   a. Oral valganciclovir is preferred
   b. Continue until 2 consecutive (-) CMV samples (1 week apart) are achieved, but not shorter than 2 weeks

2. In severe or life-threatening disease, oral formulation not tolerated, or its oral absorption may be suboptimal
   a. IV ganciclovir is preferred
   b. Treat for at least 21 days, must have at least 2 weeks of negative CMV samples and clinical resolution of symptoms
   c. May switch to PO valganciclovir when patient improving

3. When treatment/induction phase is complete (dosing table below), change to maintenance/prophylactic dosing for either non-severe or severe disease (see dosing in table above)
   a. 1 month for non-severe
   b. 3 months for severe disease or high-risk recurrence

   Consider longer therapy for patients with on-going aggressive immunosuppression
Adjustment for renal dysfunction for induction treatment dosing:

<table>
<thead>
<tr>
<th>Estimated CrCl (mL/min)</th>
<th>Valganciclovir (Valcyte)</th>
<th>Ganciclovir (Cytovene)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 70</td>
<td>900 mg PO twice a day</td>
<td>5 mg/kg IV twice a day</td>
</tr>
<tr>
<td>50-70</td>
<td>900 mg PO twice a day</td>
<td>2.5 mg/kg IV twice a day</td>
</tr>
<tr>
<td>30-49</td>
<td>450 mg PO twice a day</td>
<td>2.5 mg/kg IV daily</td>
</tr>
<tr>
<td>10-29</td>
<td>450 mg PO daily</td>
<td>1.25 mg/kg IV daily</td>
</tr>
<tr>
<td>&lt; 10</td>
<td>450 mg PO q 48 h</td>
<td>1.25 mg/kg IV q 48 h</td>
</tr>
</tbody>
</table>
True or False

CMV infection is a sign of over-immunosuppression
CMV infection

• Reduce or discontinue the antimetabolite
• May not need valganciclovir
• Can give CMV IgG (Cytogam) for invasive disease
Experimental CMV antivirals

- Maribavir
- Letermovir
- Brincidofovir – lipid conjugated cidofovir
CMV vaccines

• Currently no vaccines available
• A number of candidates are under investigation
THANK YOU FOR YOUR LISTENING

DO YOU HAVE ANY QUESTIONS?