Donor-Derived and Recipient Infections in Solid Organ Transplantation

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Northwestern University
Comprehensive Transplant Center

Viruses in May

Carrington Hotel – Katoomba, NSW – May 13, 2011
Disclosures

- **Research Support°**
  - ADMA, Adamas, BioCryst, Chimerix, GlaxoSmithKline, Roche, ViraCor*
- **Paid Consultation**
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  - BioCryst, Biota, Cellex, Clarassance, GlaxoSmithKline, MP Bioscience*, NexBio, Roche, Toyama, T2 Diagnostics*
- **Data & Safety Monitoring Board Participation**
  - Chimerix, NexBio

As of 4/17/11; ° Paid to Northwestern University; *Related to topic.
Acknowledgment

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Donor-Derived & Recipient SOT Infections

- Transplantation in Australia
- Key concepts in approaching a transplant patient with an infection
- Review of critical drug interactions
- General approach to common problems
  - Donor-derived infections
  - Fever
  - CMV
  - BK Virus
More Organs Needed than Available

Deceased Donors
Transplants
Waiting List

Principles of Transplant Infectious Diseases

CMV

Toxoplasmosis

Aspergillus
Basic Concepts of Transplant ID

• Risk Factors for Infection
  – Epidemiologic Exposure
  – Net State of Immunosuppression
    • Immunosuppressive therapy: dose, duration, temporal sequence
    • Underlying immune deficiency: autoimmune, functional
    • Integrity of mucocutaneous barriers (catheters, mucositis)
    • Devitalized tissue, fluid collections
    • Neutropenia/lymphopenia
    • Metabolic Conditions: uremia, malnutrition, DM, cirrhosis
    • Infection with immunomodulating viruses: CMV, EBV, HBV, HCV, HIV

Overview of Post-Transplant ID

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

Recipient-Derived Infection
- Transplantation

Common Infections in Solid-Organ Transplant Recipients

- <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, rhadovirus (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, V2V, 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)

Basic Concepts of Transplant ID

- MUST make a diagnosis
- Invasive procedures are almost always required
- Hit Hard & Hit Early
- Kidney Function is Abnormal
- Consider Adrenal Insufficiency
- Always lower Immunosuppression
Key Immunosuppressives: Interactions

- **Calcinurin Inhibitors (P450)**
  - Increase Levels
    - Macrolides
    - Fluoroquinolones
    - Azole antifungals (Caspo/CyA interaction)
    - Ceftriaxone
  - Decrease Levels
    - INH
    - Nafcillin
    - Rifamycins

- **Synergistic Nephrotoxicity**
  - Aminoglycosides
  - Amphotericin

- **Azathioprin/MMF**
  - Cidofovir
  - Leflunomide
Common Post-Transplant Infections
Donor-Derived Infections
Donor-Derived Infections

• Any infection of a recipient that results from an infection present in the donor and transmitted by the donated organ
• Incidence: unknown
• Types:
  – Expected: EBV, CMV, Toxo
  – Unexpected
    • LCMV, Rabies, malaria
    • Bacterial, fungal pathogens
Case 1: *Something Rare?*

- 54 yo WM with HBV/HCV/HCC
- Day 5: Fever to 102.4, mild frontal HA since time of transplant
- IS: ATG, Tacrolimus, Azathioprine
- Abx: Pip-Tazo, HB Ig, 3TC, Famciclovir, TMP-SMX
- SH: Suburbs, Iron worker
- PE: Non-focal except for a tender RUE peripheral IV catheter
Case 1: **Something Rare?**

- Continued with fever, LFTs increased
- Seizure (?) Hypoxemic
- Progressive “sepsis” with elevated LFTs and renal dysfunction
- Call from another Transplant ID doctor: “how is your recipient doing?”
Case 1: *Something Rare?*

- **Donor**
  - Previously healthy woman who was brain dead secondary to a hemorrhagic stroke
  - Donated liver, lungs, kidneys, corneas, skin
  - Purchased a hamster for her son a few weeks prior to death
The Culprit

Case 2: Something Common?

- Patient is a 56 yo WM
- Underwent OHT November 2005
  - Toxo D+/R−, CMV D+/R−
  - Pyramethamine-Sulfadiazine
  - Valganciclovir
- 9 days post-transplant
  - Donor has + blood cultures drawn the day prior to donation
  - Positive for *Pseudomonas aeruginosa*
Case 2: Something Common?

- Positive result on cultures
  - Day of transplant
  - Took several days to convey results to recipient centers
  - Patient was receiving ciprofloxacin for a probable UTI, which covered the bacteria with no serious sequellae
Case 3: Refocusing on Risk

- One recipient was identified with post-transplant HCV & HIV infection with no obvious risk factors and negative pre-transplant testing.
- Reported to OPO, UNOS, and CDC.
- Donor:
  - Negative serology for HIV & HCV.
  - Appropriately labeled as “high risk” by PHS guidelines.
  - Subsequent testing of post-transfusion serum was + for HIV and HCV by PCR.
- All other recipients tested positive for HIV and HCV.
Case 4: Living Donors

FIGURE. Timeline of events involving HIV transmission from a living organ donor — New York City, 2009

Abbreviations: HIV = human immunodeficiency virus; EIA = HIV enzyme immunoassay; HCV = human immunodeficiency virus; NAT = nucleic acid test; WB = HIV Western blot; WBC = white blood cell; DOHMH = New York City Department of Health and Mental Hygiene.

MMWR. 2011; 60: 297-301.
Current Epidemiology of DDD

- Available Sources of Data
  - Literature (publication bias)
  - US Reporting Systems
    - Disease Transmission Advisory Committee
    - OPTN/UNOS Patient Safety System
    - US Public Health Service
  - Other Reporting Systems
    - Only France has a system in place with reporting capacity that is currently publically available
DTAC: Workflow

- Report made to Patient Safety Staff
  - Prepare summary of event
  - Redact identifiers
  - Upload key materials to SharePoint Server
- E-mail based discussion
  - Initial e-mail sent to all members
  - Ongoing electronic discussion
- Day 45 Follow-up Reports submitted
- Monthly conference calls
- Bi-Annual Meetings
- Special Cases
  - Reportable Diseases: Inform CDC
  - Event-Specific Conference Calls
# DTAC Members as of July 2010

<table>
<thead>
<tr>
<th>Chair: Dr. Emily Blumberg (TID)</th>
<th>Vice Chair: Dr. Michael Green (Peds TID)</th>
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<td>Dr. Daniel Kaul (TID)</td>
<td>Ms. Alison Smith (OPO)</td>
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<td>Dr. Afshin Ehsan (Thoracic TX Surgeon)</td>
<td>Dr. Michael Nalesnik (TX Pathologist)</td>
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<td>Dr. Jon Gockerman (TX Oncology)</td>
<td>Dr. Daniel Lebovitz (Ped Critical Care, OPO)</td>
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<td>Dr. Betsy Tuttle Newhall (Abd TX Surgeon)</td>
<td>Dr. Brahm Vasudev (TX Physician)</td>
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<td>Dr. Timothy Pruett (Abd TX Surgeon)</td>
<td>Dr. Rachel Miller (TID)</td>
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<td>Dr. Matthew Yeh (TX Pathologist)</td>
<td>Ms. Carrie Comellas (TX Coordinator)</td>
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<td>Mr. Barry Friedman (TX Administrator)</td>
<td>Dr. Lewis Teperman (TX Surgeon)</td>
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<td>Ms. Linda Weiss (Dir of OPO Lab Services)</td>
<td>Dr. Michael Ison (Ex Officio, Past Chair)</td>
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<tr>
<td>Dr. Jim Bowman (Ex Officio, HRSA)</td>
<td>Dr. Bernard Kozlovsky (Ex Officio, HRSA)</td>
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<td>Dr. Matt Kuehnert (Ex Officio, CDC)</td>
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**OPTN Staff:** Shandie Covington, Robert Metzger, MD, Kimberly Parker, Sarah Taranto, Kimberly Taylor, RN

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**UNOS DONATE LIFE**
Defining What to Track & Report

- **Imputability Assessment (DTAC):**
  - **Proven:** Disease in donor and at least one recipient
  - **Probable:** Disease in one or more recipients with suggestive data about the donor
  - **Possible:** Evidence to suggest but not prove transmission
  - **Intervention without Documented Transmission (IWDT):** No transmission occurred typically because antimicrobials were used
  - **Unlikely:** Limited evidence to suggest transmission could have occurred but no transmission documented
  - **Excluded:** Alternative explanation for event

**Other reported malignancies without confirmed transmission:** angiomyolipoma, astrocytoma, breast, colon carcinoma, dermatofibrosarcoma protuberans, Kaposi’s sarcoma, leukemia, medulloblastoma, mesothelioma, myeloid sarcoma, pinealoblastoma, liposarcoma, gastrointestinal stromal tumor (GIST) spindle cell CNS carcinoma, carcinoma not otherwise specified (4), urothelial carcinoma.

<table>
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<tr>
<th>Malignancy</th>
<th># of Donor Reports</th>
<th># of Recipients with Confirmed Transmission</th>
<th># of DDD-Attributable Recipient Deaths</th>
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<tr>
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<td>Glioblastoma Multiforme</td>
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<td>1</td>
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<td>Neuroendocrine</td>
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<td>Pancreas</td>
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<tr>
<td>Ovarian Carcinoma</td>
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<td>2</td>
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<tr>
<td>Other **</td>
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<td><strong>Total Malignancies</strong></td>
<td><strong>185</strong></td>
<td><strong>34</strong></td>
<td><strong>17</strong></td>
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## Infection Reports: 2005-2010

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<th>Disease</th>
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<th># of Recipients with Confirmed Transmission</th>
<th># of DDD-Attributable Recipient Deaths</th>
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<td>Virus°</td>
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<td>Bacteria*</td>
<td>75</td>
<td>31</td>
<td>9</td>
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<tr>
<td>Fungus°</td>
<td>56</td>
<td>37</td>
<td>10</td>
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<tr>
<td>Mycobacteria§</td>
<td>37</td>
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<td>2</td>
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<tr>
<td>Parasitic†</td>
<td>30</td>
<td>18</td>
<td>6</td>
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<tr>
<td><strong>Total Infections</strong></td>
<td><strong>320</strong></td>
<td><strong>131</strong></td>
<td><strong>36</strong></td>
</tr>
</tbody>
</table>

° Viruses: Adenovirus, HBV, HCV, HEV, HIV, HTLV, herpes simplex, influenza, LCMV, Parainfluenza (PIV)-3, Parvovirus B19, rabies, West Nile Virus


§ Mycobacteria: Tuberculosis, Non-TB Mycobacteria

†Parasites: Babesia, *Balmuthia mandrillaris*, Chagas (*Trypanosoma cruzi*), *Naegleria fowleri*, schistosomiasis, strongyloides
Lessons Learned

• Donor Testing
  – False positive results occur (15)
    • Often with supplemental tests (tissue)
  – False negative results
    • 4/6 instances resulted in infectious disease transmission (HBV, HCV, HIV)
    • 2 cases reported in the literature
      – HIV/HCV co-transmission to 4 recipients
      – HIV transmitted to 1 living-donor recipient

• Increased complexity of living donor
  – May affect risk of disease transmission

• Increased challenges to communication

Unique Donor Issues in Organs

- Restricted timeline
- Different Screening Paradigm
  - No expectation for “Zero Risk”
- Donor history
- Serology-based Screening
- Variable NAT capacity and practice
- Hemodilution is a common problem
- Incomplete Data Collection
Screening for Infectious Diseases

<table>
<thead>
<tr>
<th>Virus</th>
<th>Sero Window</th>
<th>NAT Window</th>
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<tr>
<td>HBV</td>
<td>60 days</td>
<td>20 days</td>
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<tr>
<td>HCV</td>
<td>70 days</td>
<td>7 days</td>
</tr>
<tr>
<td>HIV</td>
<td>23 days</td>
<td>7 days</td>
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</table>

Critical Balance

Organ Availability

Patient Safety
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<tr>
<th>Risk per 10,000 donors</th>
<th>HIV ELISA</th>
<th>HIV NAT</th>
<th>HCV ELISA</th>
<th>HCV NAT</th>
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<tr>
<td>Window Period</td>
<td>22 days</td>
<td>9 days</td>
<td>66 days</td>
<td>7 days</td>
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<tr>
<td>Men who have sex with men</td>
<td>8.3</td>
<td>3.4</td>
<td>36.0</td>
<td>3.8</td>
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<tr>
<td>IV Drug Users</td>
<td>12.9</td>
<td>5.3</td>
<td>350.0</td>
<td>37.8</td>
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<tr>
<td>Hemophiliacs</td>
<td>0.05</td>
<td>0.02</td>
<td>0.46</td>
<td>0.05</td>
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<tr>
<td>Prostitutes</td>
<td>2.9</td>
<td>1.2</td>
<td>107.8</td>
<td>11.5</td>
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<tr>
<td>Partner with the above</td>
<td>2.7</td>
<td>1.1</td>
<td>126.2</td>
<td>13.5</td>
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<td>Blood product exposure</td>
<td>1.3</td>
<td>0.5</td>
<td>22.0</td>
<td>2.3</td>
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<tr>
<td>Incarceration</td>
<td>1.5</td>
<td>0.6</td>
<td>68.6</td>
<td>7.3</td>
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</tbody>
</table>

Clinical Approach: Fever
Clinical Approach: Fever

- Differential Diagnosis
  - Infectious
    - Think of time frame post-transplant, epidemiology
    - Viral replication:
      - CMV, EBV, HHV6, HHV7
      - Respiratory Viral Infections (influenza, PIV, RSV, adeno)
    - Bacterial
    - Fungal
    - Parasitic
  - Malignancy: PTLD
  - Drug: Drug fever, TENs/Stevens-Johnson
  - Rejection
  - Graft-versus-Host Disease
Clinical Approach: Fever

- Initial Management
  - Search for a source
    - Detailed H&P
    - Blood and urine cultures with UA (± sputum)
    - Chest X-ray (consider CT if pulmonary symptoms)
    - CMV Viral Load/Antigenemia
    - Stool cultures and C. difficile assay if diarrhea
  - Strongly consider empiric antibiotics as soon as cultures obtain
    - Consider allergies
    - Consider drug interactions
    - Consider probable source
  - Reduce immune suppression if infection probable
CMV: Cascade of Events

- Fever
- Activates & attracts PMNs
- IE enhancer region
- NF-κB
- pp65
- pp50
- IL-1

Primary site of lytic replication: Vascular Endothelium!
Current Burden of CMV Disease: D+/R-

- Kidney
- Liver
- Heart
- Lung
- Pancreas

No Prophylaxis
Prophylaxis

CMV Diagnostics

- Serology
- Culture/Shell Vial
- Antigenemia assay
  - 1 cell = ~5,000 copies
  - Neutropenia
  - Reader dependent
- PCR
- Pathology

CMV Prophylaxis Strategies

• **Universal prophylaxis**
  – Administration of antiviral agents to all individuals at risk for a fixed duration
  – May increase cost, toxicity, risk of resistance

• **Preemptive therapy**
  – Administration of antiviral therapy in response to a positive microbiologic assay or clinical scenarios
  – Requires careful monitoring, close patient contact, and use of highly sensitive, quantitative assay
  – 41% missed screening before onset

Prophylaxis vs. Pre-Emptive

Prophylaxis vs. Pre-Emptive

- **Prophylaxis**
  - **Positives**
    - Lower rate of CMV
    - Lower rejection & graft loss
  - **Negatives**
    - Drug costs
    - Drug toxicity
    - Late onset CMV
    - Resistance

- **Pre-Emptive**
  - **Positives**
    - Low drug costs
    - Low toxicity
    - “No” late onset CMV
    - “No” resistance
  - **Negatives**
    - More CMV
    - More indirect effects
    - Infection may occur if no monitoring occurs
Prophylactic Agents: Valganciclovir


- 2.9% vs. 10.4% at 100 d (p = 0.001)
- 48.5% vs. 48.8%
Study: CMV D+/R- Renal Transplant Recipients

CMV Disease

• CMV Viremia (no symptoms)
• CMV Syndrome
  – Fever, Neutropenia, Viremia
• End Organ Disease
  – Can affect any organ, esp transplant
  – Special Sites – disease without viremia
    • Gastrointestinal tract
    • CNS (including eye)
    • Testes
Ganciclovir vs. Valganciclovir

Antiviral Resistance: **UL97**

### TABLE 1. UL97 resistance mutations confirmed by marker transfer or recombinant phenotyping

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<th>Codon no.</th>
<th>Amino acids (mutation)</th>
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<th>GCV ratio†</th>
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<tr>
<td>605</td>
<td>C</td>
<td>S</td>
<td>1</td>
<td>1.9</td>
<td>41, 132, 173</td>
<td></td>
</tr>
<tr>
<td>605</td>
<td>C</td>
<td>W</td>
<td>1</td>
<td>1.9</td>
<td>41, 132, 173</td>
<td></td>
</tr>
<tr>
<td>607</td>
<td>C</td>
<td>Y</td>
<td>1</td>
<td>1.9</td>
<td>41, 132, 173</td>
<td></td>
</tr>
</tbody>
</table>

* Boldface indicates the seven most common ("vaccine") UL97 mutations conferring GCV resistance.

† Number of distinct isolates in a total of 322 cases reported in several series (20, 28, 56, 74, 132, 173, 180, 209). No number is shown for the unusual mutations reported outside these series.

‡ IC₅₀ of mutant/WT of wild type. These ratios may fluctuate by 22 to 30% in replicate assays of the same mutation, and a range is shown when reported results vary by more than this amount.

IDT indicates the designated codon and continuing through the number of codons shown. Deletion of codon 591 to 596 results in the same mutant virus as deletion of codon 190 to 205.

NA, not available.

*Vaccinia virus recombinants do not have GCV IC₅₀ ratios.

---

FIG. 2. Map of the kinase subdomain of the **UL97** gene. (A) Conserved functional regions of the UL97 kinase (pUL97). Codons defined for each region are as follows: region I, 338 to 345; region II, catalytic lysine 355; region III, glutamate 380; region IV, 453 to 462; region VII, 481 to 483; region VIII, 520 to 527; and region IX, 574 to 579 (34, 89). (B) Confirmed mutations are color coded by resistance profile. Multiple mutations at a single codon are listed in order of frequency. Map units correspond to codons of **UL97**.

Antiviral Resistance: **UL54**

**A**

3'-5' Exonuclease

Polymerization

ExoI  IV/ExoII  δC/ExoIII  II  VI  III  I  VII  V

Accessory Protein Binding

**B**

- GCV<sup>R</sup>/CDV<sup>R</sup>
- FOS<sup>R</sup>
- FOS<sup>R</sup>/GCV<sup>R</sup>
- FOS<sup>R</sup>/GCV<sup>R</sup>/CDV<sup>R</sup>
- CDV<sup>R</sup>

<table>
<thead>
<tr>
<th></th>
<th>L02M</th>
<th>L775M</th>
<th>V787I</th>
<th>V787L</th>
</tr>
</thead>
<tbody>
<tr>
<td>L510I</td>
<td>N405K</td>
<td>L405K</td>
<td>N104K</td>
<td>T503I</td>
</tr>
<tr>
<td>N495K</td>
<td>L501I</td>
<td>L516R</td>
<td>F412C/V</td>
<td>I521S</td>
</tr>
<tr>
<td>K513E/N</td>
<td>T503I</td>
<td>L516R</td>
<td>D301N</td>
<td>P522A/S</td>
</tr>
<tr>
<td>N408D/K</td>
<td>N410K</td>
<td>F412C/V</td>
<td>L516R</td>
<td>D301N</td>
</tr>
<tr>
<td>T700A</td>
<td>V715M</td>
<td>G841A</td>
<td>DI981-2</td>
<td></td>
</tr>
<tr>
<td>L802M</td>
<td>L775M</td>
<td>V787I</td>
<td>V787L</td>
<td></td>
</tr>
<tr>
<td>K805Q</td>
<td>V812L</td>
<td>A809V</td>
<td>T813S</td>
<td></td>
</tr>
<tr>
<td>T821I</td>
<td>B812L</td>
<td>A834P</td>
<td>T838A</td>
<td></td>
</tr>
</tbody>
</table>

**C**

Map units in codons

FIG. 5. Map of the DNA polymerase gene. (A) Functional regions of HCMV DNA polymerase. Codon ranges for each region are as follows: region IV/ExoII, 379 to 421; region delta-C/ExoIII, 492 to 588; region II, 696 to 742; region VI, 771 to 790; region III, 805 to 845; region I, 905 to 919; region VI, 962 to 970; and region V, 978 to 988 (190, 214). (B) Confirmed mutations color coded by resistance profile. (C) Polymorphisms observed in drug-sensitive isolates. Map units correspond to codons of the DNA polymerase gene (UL54, pol).

BK Virus

Impair cell cycle and DNA repair pathways

**BK: Risk Factors for BKVN**

*Table 1. Risk factors for the development of BKVN after renal transplantation*  

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Patients</th>
<th>BKVN (n [%])</th>
<th>Risk Factors</th>
<th>( P )</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997 to 2000</td>
<td>444</td>
<td>40 (4)</td>
<td>HLA mismatches</td>
<td>0.001</td>
<td>Awadhala <em>et al.</em> (29)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Previous acute rejection</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Use of antilymphocyte therapy</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>1997 to 2002</td>
<td>100</td>
<td>3 (3)</td>
<td>Recipient’s humoral deficiency (BKVIgG)</td>
<td>&lt;0.05</td>
<td>Ginevri <em>et al.</em> (28)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MMF use at baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000 to 2004</td>
<td>1027</td>
<td>74 (7)</td>
<td>Recipient age</td>
<td>&lt;0.05</td>
<td>Khamash <em>et al.</em> (64)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Recipient age &gt;55</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Donor female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1999 to 2001</td>
<td>286</td>
<td>9 (3.1)</td>
<td>Recipient race (white)</td>
<td>0.007</td>
<td>Rocha <em>et al.</em> (70)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Recipient gender (male)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Increase tacrolimus level</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>1984 to 2002</td>
<td>173</td>
<td>6 (3.5)</td>
<td>Recipient seronegativity</td>
<td>0.01</td>
<td>Smith <em>et al.</em> (27)</td>
</tr>
<tr>
<td>1996 to 2003</td>
<td>1001</td>
<td>41 (4)</td>
<td>No risk factors</td>
<td></td>
<td>Vasudev <em>et al.</em> (67)</td>
</tr>
</tbody>
</table>

*Race and gender (recipient); age and race (donor); cold ischemia time, panel-reactive antibodies, previous transplant, cadaver versus living donor, and kidney versus kidney-pancreas (transplant); and delayed graft function, use of IL-2 receptor blocker, and maintenance immunosuppression cyclosporine versus tacrolimus (posttransplantation) were not identified as risk factors for the occurrence of BKVN.*

**Other identified risk factors include:** stent placement, DM

BK: **Clinical Presentation**

![Graph showing the probability of BK replication, viremia, and nephropathy over weeks after transplantation.](image)

BK: Screening

- At time of any biopsy
- With any renal dysfunction
- Year 1-2
  - Q3 month screening
- Year 3-5
  - Annual screening

**BK: Screening**

- **Impact of Screening**
  - Typically screening is linked with reduction in immune suppression
  - Associated with lower rate of progression to BKVN
  - Associated with improved graft survival

**Actuarial Graft Survival with BKVN**

<table>
<thead>
<tr>
<th>Time Period</th>
<th>1 yr</th>
<th>3 yr</th>
<th>5 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Screening</td>
<td>89.5%</td>
<td>57.9%</td>
<td>47.4%</td>
</tr>
<tr>
<td>Screening</td>
<td>94.8%</td>
<td>68.4%</td>
<td>57.6%</td>
</tr>
</tbody>
</table>

## BK: Reduction of IS

**TABLE 5.** Treatment of PVAN by modification of maintenance immunosuppression

<table>
<thead>
<tr>
<th>Switching</th>
<th>Decreasing</th>
<th>Discontinuing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tacrolimus→CsA (trough levels 100–150 ng/mL)</td>
<td>Tacrolimus (trough levels &lt;6 ng/mL)</td>
<td>Tacrolimus or MMF (maintain or switch to dual drug therapy):</td>
</tr>
<tr>
<td>(B-III)</td>
<td>(B-III)</td>
<td>CsA/prednisone (B-III)</td>
</tr>
<tr>
<td>MMF→azathioprine (dosing ≤100 mg/d)</td>
<td>MMF dosing ≤1 g/day</td>
<td></td>
</tr>
<tr>
<td>(B-III)</td>
<td>(B-III)</td>
<td></td>
</tr>
<tr>
<td>Tacrolimus→sirolimus (trough levels &lt;6 ng/mL)</td>
<td>CsA (trough levels 100–150 ng/mL)</td>
<td>Tacrolimus/prednisone (B-III)</td>
</tr>
<tr>
<td>(C-III)</td>
<td>(B-III)</td>
<td></td>
</tr>
<tr>
<td>MMF→sirolimus (trough levels &lt;6 ng/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(C-III)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMF→leflunomide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(C-III)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PVAN, polyomavirus-associated nephropathy; CsA, cyclosporine A; MMF, mycophenolate mofetil.
BK: **Treatment**

- **Challenges:**
  - BK replication is dependent on host cell factors
  - Except for T Ag DNA helicase, there are no virally encoded antiviral drug targets such as thymidine kinase or viral DNA polymerase

- **Option**
  - Alterations in Immune Suppression
  - Cidofovir
  - Leflunomide
  - Fluoquinolones
  - IgIV

Questions?

I am a registered organ donor!
Are you?