Infections in renal transplantation

S. Van Laecke,
University Hospital of Ghent, Belgium
Mortality following kidney transplantation

- Infection: 20%
- Malignancy: 13%
- Other: 7%
- Cardiovascular: 37%
- Cerebrovascular: 23%
INFECTION rate IN HIV....
Yearly opportunistic infection rates per 1,000 person-years

CDC Adult and Adolescent Spectrum of Disease Project...Morris 2004
Not close to infection rate in kidney transplants in the nineties

Dhamdiksharaka VR et al. Transplantation 2006
**Table 1. Factors Affecting the Net State of Immunosuppression in Transplant Recipients.**

- Immunosuppressive therapy: dose, duration, and temporal sequence
- Underlying immune deficiency: autoimmune disease, functional immune deficits
- Integrity of the mucocutaneous barrier: catheters, epithelial surfaces
- Devitalized tissue, fluid collections
- Neutropenia, lymphopenia
- Metabolic conditions
  - Uremia
  - Malnutrition
  - Diabetes
  - Alcoholism with cirrhosis
- Infection with immunomodulating viruses
  - Cytomegalovirus
  - Epstein–Barr virus
  - Hepatitis B and C viruses
  - Human immunodeficiency virus
Causes of death and death rates in renal transplant patients.

United States Renal Data System. USRDS 1998 Annual Data Report
Infection-Related Mortality in a Large Cohort of Renal Transplant Recipients

Linares L et al. Transplantation Proceedings 2007
Cumulative Risk for Infection-related Death Post Transplant: Antibody Induction

Within 6 months RR=1.32
After 6 months RR=1.16

Meler-Krissche et al. JASN 2002;13:789
Increased incidence of infections following the late introduction of MMF in renal transplant recipients.

Sites of infections (by patient numbers) pre-conversion and post-conversion to MMF

Risk of Infectious Death Post Transplant: Impact of Allograft Function

Infection risk according to the Symphony Study

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Standard-Dose Cyclosporine (N=384)</th>
<th>Low-Dose Cyclosporine (N=405)</th>
<th>Low-Dose Tacrolimus (N=403)</th>
<th>Low-Dose Sirolimus (N=380)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood or lymphatic</td>
<td>33.3</td>
<td>33.6</td>
<td>36.2</td>
<td>36.1</td>
</tr>
<tr>
<td>Anemia</td>
<td>18.5</td>
<td>17.4</td>
<td>12.1</td>
<td>25.0</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>10.2</td>
<td>10.3</td>
<td>13.4</td>
<td>10.1</td>
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<tr>
<td>Gastrointestinal</td>
<td>33.3</td>
<td>37.6</td>
<td>43.4</td>
<td>34.7</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1.9</td>
<td>4.2</td>
<td>5.2</td>
<td>2.6</td>
</tr>
<tr>
<td>Constipation</td>
<td>6.5</td>
<td>5.2</td>
<td>6.7</td>
<td>6.1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13.6</td>
<td>11.0</td>
<td>25.3</td>
<td>19.5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4.7</td>
<td>3.9</td>
<td>5.5</td>
<td>7.6</td>
</tr>
<tr>
<td>General or site of drug administration</td>
<td>23.2</td>
<td>22.6</td>
<td>22.1</td>
<td>27.4</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>17.0</td>
<td>17.5</td>
<td>14.2</td>
<td>18.7</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>4.4</td>
<td>3.6</td>
<td>5.0</td>
<td>9.0</td>
</tr>
<tr>
<td>Opportunistic infection</td>
<td>26.0</td>
<td>22.8</td>
<td>20.9</td>
<td>20.3</td>
</tr>
<tr>
<td>Candida</td>
<td>7.6</td>
<td>4.7</td>
<td>3.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>14.3</td>
<td>11.0</td>
<td>9.7</td>
<td>6.1</td>
</tr>
<tr>
<td>Herpes simplex virus</td>
<td>5.5</td>
<td>1.7</td>
<td>4.5</td>
<td>5.1</td>
</tr>
<tr>
<td>Other infection or infestation</td>
<td>5.2</td>
<td>50.3</td>
<td>52.4</td>
<td>59.6</td>
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<tr>
<td>Nasopharyngitis</td>
<td>5.7</td>
<td>7.8</td>
<td>2.9</td>
<td>4.0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>4.1</td>
<td>1.7</td>
<td>5.7</td>
<td>5.0</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>28.4</td>
<td>23.8</td>
<td>23.6</td>
<td>23.2</td>
</tr>
</tbody>
</table>

Ekberg H et al. NEJM 2007
Time Course and Frequency of Infections after Transplantation
Time Course of Urinary Tract Infections by the Causative Uropathogen
Risk factors for patients at risk of urinary tract infections after renal transplantation

Long period of haemodialysis before transplantation
Female sex
Indwelling catheterization
Urinary tract infection before kidney transplantation
Vesicoureteral reflux
Polycystic kidney disease with a history of recurrent UTI without binephrectomy before grafting
Diabetes mellitus
Chronic viral infections
Increased urinary aluminium excretion

UTI, urinary tract infection.

Time to first UTI according to sex in US Renal Transplant patients (1996-2000)

Abbott KC et al. AJKD 2004
Acute Pyelonephritis Represents a Risk Factor Impairing Long-Term Kidney Graft Function
Acute Pyelonephritis Represents a Risk Factor Impairing Long-Term Kidney Graft Function

Pelle et al. AJT 2007
The Incidence of Pneumonia Before and After Renal Transplantation

Kutinova et al. AJT 2006
Cytomegalovirus

- **CMV infection**: isolation of CMV or detection of viral proteins or nucleic acids in any body fluid or tissue specimen

- **CMV disease**: the presence of signs and/or symptoms of tissue injury combined with virus isolation and/or histopathologic or immunochemical evidence of CMV in tissue samples

![Graph of CMV infection probabilities over time](Dmitrienko et al. KI 2007)
CMV End-Organ Disease

- Pneumonia
- Retinitis (late manifestation of the consequence of CMV infection and invasion)
- Pancreatitis
- Nephritis
- Cystitis
- Hepatitis
- Gastrointestinal disease
- Myocarditis
- Central nervous system disease (rare in transplant recipients)
CMV pneumonia

Lung: frequently lethal
- all patterns (interstitial, alveolar, symmetrically, lower lobes > unilaterally, localised)
- Gradual, over days, association with PCP
- When rapid evolution (12-24 h) to respiratory insufficiency: coinfection (bacterial, fungal)

Courtesy of Ajit Limaye, MD.
CMV: clinical effects

- **Direct**: tissue-damage
- **Indirect**: immunomodulation
  - higher ‘net state of immunosuppression’
  - role in acute rejection (controversial)
  - role in chronic allograft injury
  - more PTLD

**Sagedal, AJT 2002**: CMV disease as predictor for acute tubulo-interstitial rejection (RR 3.1)

**Lowance, NEJM 1999**: prophylaxis with valacyclovir: acute allograft rejection in D+/R-: minus 50%.

**Mechanisms**
- Upregulation of MHC II antigens on allograft
- Enhancing adhesion molecules (eg. ICAM-1) on endothelium
- Release of large array of cytokines

Lowance et al. NEJM 1999
CMV AND CAN
POSSIBLE MECHANISMS

CMV → Proinflammatory cytokines
       ↓ IL-1
       ↓ TNF-α
       ↓ TGF-β
       ↓ PDGF

CAN: SMC-proliferation
Matrix protein synthesis

AR → Anti-rejection therapy
CMV

Replication

Amplification / Dissemination

MHC Restricted, CMV specific T cells
Risk factors for Mortality >100 days Post Transplantation

- CMV infection, $P < 0.001$
- CMV disease, $P = 0.006$
- Patient age, $P < 0.001$
- Death censored graft loss in whole study period, $P < 0.001$
- Death censored graft loss first 100 days after Tx, $P = 0.08$

Sagedal et al. KI 2004.
Incidence of CMV Disease by D/R - status

Oral ganciclovir (1000mg TID) for 3m in D-R+ and 6m in D+/R+ and D+/R-
Five-year Graft Survival in Patients with CMV Disease and a Functioning Graft at 6 Months

Oral ganciclovir (1000mg TID) for 3m in D-R+ and 6m in D+/R+ and D+/R-

Schnitzler et al. JASN 2003;14:780.
## Effects of Different Immunosuppressive Drugs on CMV

<table>
<thead>
<tr>
<th>Drug</th>
<th>Activation From Latency</th>
<th>Amplification of Replicating Virus</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATG, OKT3</td>
<td>4+</td>
<td>1-2+</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>1+</td>
<td>1-2+</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>1+</td>
<td>1-2+</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>0</td>
<td>4+</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>0</td>
<td>4+</td>
</tr>
<tr>
<td>Prednisone</td>
<td>0</td>
<td>2-3+</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>0</td>
<td>3+</td>
</tr>
</tbody>
</table>
CMV and immunosuppressive treatment

Differential effects of prednisolone and azathioprine on the development of human cytomegalovirus replication post liver transplantation.

<table>
<thead>
<tr>
<th>BASELINE IMMUNOSUPPRESSION</th>
<th>RR</th>
<th>95%CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TACRO</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>TACRO+PRED</td>
<td>4.34</td>
<td>2.03-9.26</td>
<td>0.0001</td>
</tr>
<tr>
<td>TACRO+PRED+AZA</td>
<td>1.61</td>
<td>0.96-2.72</td>
<td>0.07</td>
</tr>
<tr>
<td>OTHER</td>
<td>2.98</td>
<td>1.6-5.55</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

Nebbia et al. Transplantation 2007
Reduced risk of cytomegalovirus infection in solid organ transplant recipients treated with **sirolimus**: a pooled analysis of clinical trials.

<table>
<thead>
<tr>
<th>Study</th>
<th>OR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>301</td>
<td>0.68</td>
<td>0.34-1.37</td>
<td>0.279</td>
</tr>
<tr>
<td>302</td>
<td>1.48</td>
<td>0.73-3.01</td>
<td>0.278</td>
</tr>
<tr>
<td>216</td>
<td>0.22</td>
<td>0.07-0.71</td>
<td>0.011</td>
</tr>
<tr>
<td>210</td>
<td>0.42</td>
<td>0.11-1.52</td>
<td>0.185</td>
</tr>
<tr>
<td>207</td>
<td>1.27</td>
<td>0.36-4.53</td>
<td>0.714</td>
</tr>
<tr>
<td>220</td>
<td>0.49</td>
<td>0.18-1.34</td>
<td>0.164</td>
</tr>
<tr>
<td>211</td>
<td>1.63</td>
<td>0.44-6.12</td>
<td>0.466</td>
</tr>
<tr>
<td>316</td>
<td>0.41</td>
<td>0.12-1.35</td>
<td>0.141</td>
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<tr>
<td>ORION</td>
<td>0.42</td>
<td>0.20-0.89</td>
<td>0.024</td>
</tr>
<tr>
<td>Pooled</td>
<td>0.64</td>
<td>0.42-1.0</td>
<td>0.047</td>
</tr>
</tbody>
</table>

Demopoulos et al. Transplantation Proceedings 2008
A lower incidence of CMV infection in *de novo* heart transplant recipients randomized to *everolimus*.

Logrank p values: 0.0002 (1.5 mg Everolimus vs. AZA) and <0.0001 (3 mg Everolimus vs. AZA).

Hill et al. Transplantation 2007
Rate of CMV Disease Despite Antiviral Prophylaxis (D+/R-)

<table>
<thead>
<tr>
<th>Renal Transplants</th>
<th>Placebo</th>
<th>Valacyclovir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis (3 mo)</td>
<td>45%</td>
<td>3%</td>
</tr>
<tr>
<td>Postprophylaxis (6 mo)</td>
<td>45%</td>
<td>16%</td>
</tr>
</tbody>
</table>

Meta-Analysis: The Efficacy of Strategies To Prevent Organ Disease by Cytomegalovirus in Solid Organ Transplant Recipients

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Odds Ratio</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
<th>Universal Prophylaxis Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balfour et al., 1999 (59)</td>
<td>0.18</td>
<td>0.04</td>
<td>0.89</td>
<td>2/53</td>
<td>9/51</td>
</tr>
<tr>
<td>Merigan et al., 1992 (52)</td>
<td>0.22</td>
<td>0.06</td>
<td>0.62</td>
<td>5/76</td>
<td>18/73</td>
</tr>
<tr>
<td>Saliba et al., 1993 (36)</td>
<td>0.23</td>
<td>0.07</td>
<td>0.76</td>
<td>4/60</td>
<td>14/60</td>
</tr>
<tr>
<td>Restaing et al., 1994 (60)</td>
<td>0.17</td>
<td>0.01</td>
<td>3.78</td>
<td>0/10</td>
<td>2/18</td>
</tr>
<tr>
<td>Kleinmayr et al., 1996 (33)</td>
<td>0.43</td>
<td>0.03</td>
<td>7.63</td>
<td>1/22</td>
<td>1/10</td>
</tr>
<tr>
<td>Poullak-Noble et al., 1996 (37)</td>
<td>0.29</td>
<td>0.09</td>
<td>0.95</td>
<td>6/24</td>
<td>14/24</td>
</tr>
<tr>
<td>Brennan et al., 1997 (61)</td>
<td>0.15</td>
<td>0.01</td>
<td>3.10</td>
<td>0/19</td>
<td>3/23</td>
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<tr>
<td>Gavaldà et al., 1997 (34)</td>
<td>0.50</td>
<td>0.13</td>
<td>1.89</td>
<td>4/37</td>
<td>7/36</td>
</tr>
<tr>
<td>Gane et al., 1997 (62)</td>
<td>0.07</td>
<td>0.01</td>
<td>0.56</td>
<td>1/150</td>
<td>13/154</td>
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<tr>
<td>Barkholt et al., 1999 (35)</td>
<td>0.31</td>
<td>0.10</td>
<td>0.97</td>
<td>7/28</td>
<td>16/72</td>
</tr>
<tr>
<td>Lowrance et al., 1999 (14)</td>
<td>0.13</td>
<td>0.04</td>
<td>0.34</td>
<td>4/206</td>
<td>21/310</td>
</tr>
<tr>
<td>Overall effect</td>
<td>0.20</td>
<td>0.10</td>
<td>0.31</td>
<td>34/794</td>
<td>126/788</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Odds Ratio</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
<th>Preemptive Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coeli et al., 1995 (63)</td>
<td>0.10</td>
<td>0.00</td>
<td>2.04</td>
<td>0/22</td>
<td>3/18</td>
</tr>
<tr>
<td>Hilberd et al., 1995 (64)</td>
<td>0.55</td>
<td>0.12</td>
<td>2.60</td>
<td>3/34</td>
<td>4/38</td>
</tr>
<tr>
<td>Brennan et al., 1997 (65)</td>
<td>1.43</td>
<td>0.08</td>
<td>24.81</td>
<td>1/15</td>
<td>1/21</td>
</tr>
<tr>
<td>Reyes et al., 2001 (66)</td>
<td>1.00</td>
<td>0.06</td>
<td>16.76</td>
<td>1/30</td>
<td>1/39</td>
</tr>
<tr>
<td>Paya et al., 2002 (67)</td>
<td>0.31</td>
<td>0.01</td>
<td>7.99</td>
<td>0/35</td>
<td>1/34</td>
</tr>
<tr>
<td>Sagdad et al., 2003 (68)</td>
<td>0.04</td>
<td>0.00</td>
<td>0.76</td>
<td>0/43</td>
<td>8/38</td>
</tr>
<tr>
<td>Overall effect</td>
<td>0.20</td>
<td>0.11</td>
<td>0.69</td>
<td>5/208</td>
<td>18/190</td>
</tr>
</tbody>
</table>

**Prophylactic trials**

- **Cautions:** Most trials were small and were not blinded.

- **Implications:** Although the authors prefer universal prophylaxis over preemptive treatment, they recommend a large confirmatory trial to directly compare the 2 strategies.

**Preemptive trials**

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Kalll AC et al, Ann Int Med 2005
Improvement in Long-Term Renal Graft Survival due to CMV Prophylaxis with Oral Ganciclovir

Klem et al. AJT 2008
Valganciclovir Mechanism of Action

VGCV = valganciclovir; GCV = ganciclovir; GCV-MP = ganciclovir monophosphate; GCV-DP = ganciclovir diphosphate; GCV-TP = ganciclovir triphosphate.

Courtesy of Mark D. Pescovitz, MD.
Valganciclovir Oral Absorption Study


![Graph showing concentration over time for different doses of valganciclovir and ganciclovir.](chart.png)
CMV: prophylaxis versus pre-emptive treatment

Time to occurrence of CMV DNA viremia.

**D+R-**

Proportion of patients without CMV DNAemia

Time to first CMV DNAemia in days

n=13

p=0.24

**D+R+**

Proportion of patients without CMV DNAemia

Time to first CMV DNAemia in days

n=22

p=0.005

**D-R+**

Proportion of patients without CMV DNAemia

Time to first CMV DNAemia in days

n=11

p=0.0135

**Study Group:**

- Preemptive
- Prophylactic

**Khoury, AJT 2008**
**CMV: prophylaxis versus pre-emptive treatment**

D+/R- Have higher CMV levels which are highest in the Preemptive group

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*Khoury, AJT 2006*
Valacyclovir prophylaxis versus preemptive valganciclovir therapy to prevent CMV disease

- Assessed for eligibility (n = 81)
  - Excluded (n = 11)
    - Not meeting inclusion criteria (n = 10)
    - Refused to participate (n = 1)
  - Randomized (n = 70)
  - Intention-to-treat population (n = 70)
  - Allocated to preemptive therapy (n = 35)
    - Received allocated intervention (n = 36)
  - Allocated to valacyclovir (n = 34)
    - Received allocated intervention (n = 34)
  - Lost to follow-up (n = 0)
  - Lost to follow-up (n = 1)
    - Death (n = 1)
  - Completed 12 months follow-up (n = 36)
  - Completed 12 months follow-up (n = 35)

Graphs showing:
- Patients free of CMV DNAemia (%)
  - Preemptive
  - Valacyclovir
  - P < 0.001 (Log-Rank)
- Patients free of biopsy-proven acute rejection (%)
  - Preemptive
  - Valacyclovir
  - P = 0.034 (Log-Rank)

Relschig T et al, AJT 2008
CMV: prophylaxis versus preemptive treatment: pro/con

- **PRO:**
  - prevention end-organ disease
  - reduction of acute rejection
  - reduction of opportunistic infections
  - improved survival

- **CON:**
  - cost
  - potential resistance
  - delayed CMV-specific T-cell responses
  - late onset CMV disease
Cost-efficiency of prophylactic versus preemptive valganciclovir

Khoury, AJT 2006
Reduction in CMV viral load with time in patients treated with oral valganciclovir or i.v. ganciclovir. There was no difference in viral load reduction rate between the treatment groups.

(cutoff level of 600 copies/mL plasma).

Asberg et al. AJT 2007
Kaplan–Meier curves showing the influence of three different baseline viral load levels on efficacy of treatment (viral eradication with cutoff level of 600 copies/mL plasma; per-protocol population) (p < 0.001, log-rank test).

Aaberg et al. AJT 2007
CMV: Mechanisms of UL97 and UL54 associated Ganciclovir resistance

CMV: resistance

Clinical failure or sustained viremia on GCV or ValGCV

Access to real time resistance testing?

No

- Iv GCV up to 10mg/kg q12h
  - Sustained viremia
  - Switch: iv FOS or iv FOS + iv GCV
    - Sustained viremia
    - Switch to CDV

Yes

- IC50 <20uM UL97 mutation
  - IC50 >20uM UL97+UL54 mutation

BK polyoma

The nephropathy is characterized by typical intranuclear viral inclusion bodies in tubular epithelial cells (arrowheads). Tubules show severe virally induced epithelial cell necrosis and denudation of basement membranes (arrows).

Bonvoisin C et al. Transplantation 2008

CAVEAT focal presentation
Type and prevalence of BK virus (BKV) infections in kidney transplant recipients.

Histologic Pattern Biopsy Findings Outcome (ESRD) Differential

A Intranuclear viral inclusions 13% Normal
Minimal inflammation tubular cell necrosis fibrosis Coexisting diagnosis

B Intranuclear viral inclusions 55% Interstitial nephritis
Moderate to severe interstitial inflammation Tubular cell necrosis

B1 B2 B3

B3 Minimal tubular atrophy and fibrosis

Acute tubular necrosis Acute rejection

C Intranuclear viral inclusions 100% Chronic allograft nephropathy
Moderate to severe tubular atrophy and fibrosis

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

Bohl DL et al cJASN 2007
BKVN

risk factors

• Immunosuppressive therapy?
  – Dose reduction can be beneficial
  – TRL, MMF, ATG, corticosteroid pulses implicated
• Rejection?
  – Many cases of preceding/coincidence with acute rejection
    • Augmentation of IS?
    • BK promoted by rejection?
    • Upregulation of MHC Ag by viral replication?
• Number of HLA mismatches?
• Age
• Gender
• Diabetes mellitus
• Serostatus donor
• HLA C7 allele
Immunosuppression and BKVN

Immune Suppression

Inadequate  Excessive

Rejection  BKV Nephropathy

Allograft dysfunction
Tubulointerstitial nephritis
Fibrosis

Bohl DL et al. CJASN 2007
Lower actuarial graft survival rates in patients with BK polyoma nephropathy.

results from the Medical College of Wisconsin 1996–2004

Hariharan S et al. KI 2006
Screening protocol based on plasma BKV DNA PCR.

- Months 1-6, 9, and 12
- Allograft dysfunction
- PCR +
- Stable Creatinine
- Decrease immunosuppression and monitor PCR biweekly until undetectable
- PCR +
- Persistent Viremia
- No BKV Nephropathy
- BKV nephropathy +/− tubulitis
- Biopsy
- Consider
  - IVIG
  - Cidofovir
  - Leflunamide
  - Quinolones

Bohl DL et al. CJASN 2007

Josephson et al. Transplantation 2006
Summary of outcomes in small series of treatment of PVAN since 2002

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cidofovir</th>
<th>Leflunomide</th>
<th>Fluoroquinolones</th>
<th>IVIg</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of reports</td>
<td>27</td>
<td>18</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>No. of patients per report</td>
<td>1–26</td>
<td>1–30</td>
<td>4–10</td>
<td>1–11</td>
</tr>
<tr>
<td>Total no. of patients</td>
<td>184&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>189&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>14</td>
<td>29&lt;sup&gt;b,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Percentage of eventually cleared viraemia</td>
<td>82/168 (49%)</td>
<td>72/148 (49%)</td>
<td>0/10 (0%)</td>
<td>15/29 (52%)</td>
</tr>
<tr>
<td>Percentage of graft loss</td>
<td>42/184 (23%)</td>
<td>32/189 (17%)</td>
<td>0/14 (0%)</td>
<td>2/29 (7%)</td>
</tr>
</tbody>
</table>

All patients also had concomitant immunosuppression dose reduction.

<sup>a</sup> Three reports included a total of 25 patients on combined cidofovir and leflunomide.

<sup>b</sup> One report included one patient on combined cidofovir and IVIg.

<sup>c</sup> Two reports included 16 patients on combined leflunomide and IVIg.
CONCLUSION

• Many studies about infections in SOT single-center, retrospective, prone to bias
• Unfortunately no trend in decrease of (bacterial/fungal) infections
• CMV: still remaining questions about
  -resistance
  -the optimal duration of both prevention and treatment
  -genotyping and the place of newer drugs in treatment and prevention
  -prophylaxis versus pre-emptive treatment: no multicenter well-designed RCT
• BK polyoma: still controversial issues such as treatment, retransplantation and screening protocols.
• Poor ability to measure alloimmune activation and net state of immunosuppression