Infections in Solid Organ Transplantation

Patrick M. Klem, PharmD, BCPS
Clinical Pharmacy Specialist – Ambulatory Care Services
University of Colorado Hospital
Outline

• CMV: prevalence, which preventative strategy (prophylaxis vs monitoring/preemptive therapy), what drugs, how long, what about ganciclovir resistance

• Polyomavirus: prevalence, outcomes, screening strategies, treatment interventions

• Hepatitis C: natural history on dialysis vs transplant, treatment options

• Hepatitis B: treatment post-transplant, use of Hep B cAg+ donors

• EBV: prevalence, outcomes, role of surveillance and preemptive treatment
### Prevalence of Solid Organ Transplants

<table>
<thead>
<tr>
<th>Type of Organ</th>
<th># in 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal –</td>
<td>16,646</td>
</tr>
<tr>
<td>Liver –</td>
<td>6,136</td>
</tr>
<tr>
<td>Heart –</td>
<td>2,147</td>
</tr>
<tr>
<td>Lung -</td>
<td>1,401</td>
</tr>
<tr>
<td>Kidney + Pancreas –</td>
<td>914</td>
</tr>
<tr>
<td>Pancreas -</td>
<td>390</td>
</tr>
<tr>
<td>Heart-Lung -</td>
<td>31</td>
</tr>
</tbody>
</table>
## Incidence of Infections

<table>
<thead>
<tr>
<th>Type of Infection</th>
<th>Liver</th>
<th>Kidney</th>
<th>Heart</th>
<th>Lung/heart-lung</th>
<th>Pancreas/KP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial</td>
<td>33-68</td>
<td>47</td>
<td>20-30</td>
<td>35-66</td>
<td>35</td>
</tr>
<tr>
<td>CMV</td>
<td>22-29</td>
<td>8-32</td>
<td>9-35</td>
<td>53-75</td>
<td>50</td>
</tr>
<tr>
<td>HSV</td>
<td>3-14</td>
<td>53</td>
<td>1-42</td>
<td>10-18</td>
<td>6</td>
</tr>
<tr>
<td>VZV</td>
<td>5-10</td>
<td>4-12</td>
<td>1-12</td>
<td>8-15</td>
<td>9</td>
</tr>
<tr>
<td>Candida sp.</td>
<td>1-26</td>
<td>2</td>
<td>1-5</td>
<td>10-16</td>
<td>32</td>
</tr>
<tr>
<td>PCP</td>
<td>4-11</td>
<td>5-10</td>
<td>1-8</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>
Immunosuppressant Medications

- **Glucocorticoids**
  - Reduce neutrophil accumulation at site of inflammation
  - Inhibit IL-2 gene promoter
- **Calcineurin inhibitors** (cyclosporine, tacrolimus)
  - Inhibit T cell function by decrease IL-2 production
- **Antiproliferative agents** (mycophenolate, azathioprine)
  - Interrupts DNA replication of T cells
- **Sirolimus**
  - Inhibit intracellular signaling pathways of IL-2 receptor
  - Induce neutropenia
Immunosuppressant Medications

- Monoclonal antibodies
  - CD3 receptor blocker (OKT3)
  - IL-2 receptor blockers (basiliximab, daclizumab)
- Polyclonal antibodies
  - Anti-thymocyte globulin (Thymoglobulin, Atgam)
Immunizations

- Hepatitis B
  - Dialysis patients require higher dose
- Hepatitis A
- Polio, inactivated
- Tetanus
- Varicella (LA)
- Influenza
  - Inhaled influenza vaccine is live attenuated
- Pneumococcal
  - Repeat every 3 – 5 years
Infectious Complications

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

Transplantation

Recipient-Derived Infection

<table>
<thead>
<tr>
<th>&lt;1 Month</th>
<th>1–6 Months</th>
<th>&gt;6 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection with antimicrobial-resistant species: MRSA, VRE, Candida species (non-albicans), Aspiration, Catheter infection, Wound infection, Anastomotic leaks and ischemia, <em>Clostridium difficile</em> colitis</td>
<td>With PCP and antiviral (CMV, HBV) prophylaxis: Polyomavirus BK infection, nephropathy, <em>C. difficile</em> colitis, HCV infection, Adenovirus infection, influenza, <em>Cryptococcus neoformans</em> infection, <em>Mycobacterium tuberculosis</em> infection, Anastomotic complications</td>
<td>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)</td>
</tr>
<tr>
<td>Donor-derived infection (uncommon): HSV, LCMV, rhabdovirus (rabies), West Nile virus, HIV, <em>Trypanosoma cruzi</em></td>
<td>Without prophylaxis: Pneumocystis, Infection with herpesviruses (HSV, VZV, CMV, EBV), HBV infection, Infection with listeria, nocardia, toxoplasma, strongyloides, leishmania, <em>T. cruzi</em></td>
<td></td>
</tr>
</tbody>
</table>
Month 0 - 1

- Recurrent infections
  - Donor and recipient
- Infectious complications related to surgery
  - Line sepsis
  - UTI from urethral stent
  - Pulmonary infections after lung transplant or prolonged ventilator support
Investigation of Rabies Infections in Organ Donor and Transplant Recipients — Alabama, Arkansas, Oklahoma, and Texas, 2004

On July 1, this report was posted as an MMWR Dispatch on the MMWR website (http://www.cdc.gov/mmwr)
Months 1 - 6

- Reactivation or primary infection of viral diseases
  - CMV, HSV, HBV, HCV, VZV, EBV
  - Polyoma virus nephropathy in renal transplant
- Emergence of opportunistic pathogens
  - Bacterial
    - Nocardia
  - Fungal
    - Candida, aspergillosis, PCP
- Higher risk of “common infections”
After 6 months

- Higher risk of “common infections”
- Continued risk of opportunistic infections
  - Endemic fungal infections
  - PCP, CMV, nocardia
- Post-transplant lymphoproliferative disorder secondary to Epstein Barr Virus
- Polyoma virus nephropathy in renal transplant
Public Health Dispatch

Multistate Outbreak of Hepatitis A Among Young Adult Concert Attendees — United States, 2003
Cytomegalovirus (CMV)

- A member of herpes virus family
- Most frequent infectious complication in renal transplant recipients
- **Infection**: CMV viremia by PCR analysis
- **Disease**: CMV viremia + clinical symptoms
  - Fever, leukopenia, increase LFTs, increase creatinine, increase LDH
  - Localized symptoms varies on type of transplant
CMV: Prevalence in an untreated population

477 consecutive KTx recipients without prophylaxis from 1994-97:

At day+100: 64% with CMV infection, 24% with CMV disease

Hartmann A et al, Transplantation 2006; 82: S15
CMV

• Antibody positive: IgG by ELISA
  – Indicated prior exposure
  – Present in 30 – 80 % of patients

• Diagnosis
  – PCR testing
  – Antigenemia
  – Biopsy
Effects of CMV

• Direct
  – Neutropenia & thrombocytopenia
  – Flu-like symptoms
  – Inflammatory response & tissue injury
  – Organ infection & accompanying symptoms

• Indirect
  – Injury or rejection of transplanted organ
    • Up regulation of HLA antigens & activation of cytokines
  – Increase risk of fungal and bacterial superinfections
CMV: How best to prevent?

- **Prophylaxis** - Therapy for all patients at risk

- **Monitoring and preemptive therapy** - periodic PCR screening and treatment only if viremic

- **Ganciclovir vs. Valganciclovir**
  - Oral: 7% vs 70% bioavailability
  - IV GCV 2.5-5.0 mg/kg/d = Valcyte 450 mg qD
Drug Therapy for CMV

- **Prophylaxis**
  - Given to all D+/R- transplants
  - Utilize during and after polyclonal/monoclonal antibody therapy for moderate risk patients

**Agents**
- Ganciclovir
- Valganciclovir
- IVIG – CMV
- Valacyclovir
Drug Therapy for CMV

• Preemptive therapy
  – Monitor CMV viral replication
  – Treat positive results with “treatment doses of antiviral therapy.”
  – Preememptive vs. prophylaxis:
    • Cost neutral
    • Equal efficacy in prevent symptomatic CMV disease
    • Requires extra monitoring

BK Virus
Polyoma Virus (BK Virus)

- DNA virus causing interstitial nephritis (nephropathy) after renal transplant
  - Can appear like acute rejection on biopsy
- BK & JC Virus
  - Primarily seen in renal transplant patients
- Developing knowledge of pathogenesis
- Infection in 10 – 45% or renal transplant
- High rate of graft failure with nephropathy
- Risk Factors
  - Over immunosuppression, age, DM, - serostatus
Prognosis after PVAN diagnosis:

- 55 cases of PVAN diagnosed from 2002-04:
  - 31 with renal dysfunction
  - 24 diagnosed by protocol biopsy

- Mean 20 month f/u:
  - 15% graft loss
  - 24% with major functional decline (>50%) from diagnosis

Wadei HM et al, Am J Transplant 2006; 6: 1025
Interventions to slow progression: does anything work?

- Possible interventions:
  - Cidofovir 0.25 mg/kg q 2 weeks x 4
  - Transition to CSA (trough 125-175 ng/ml) vs reduction of TAC (4-6 ng/ml) combined with reduction of MMF (250 mg BID)
  - IVIg 1.25 g/kg x 2

- None demonstrated a benefit
Lefunomide +/- cidofovir in addition to immunosuppression reduction

- 26 patients with biopsy-proven BKVAN:
  - 17 leflunomide alone
  - 9 leflunomide + cidofovir
    - Leflunomide: started at 100 mg/d x 3, then 20mg/d with goal trough 50-100 ng/ml
    - Cidofovir: started at 0.25mg/kg IV biweekly x 4 doses

Josephson M et al, Transplantation 2006;81: 74
Lefunomide +/- cidofivir in addition to immunosuppression reduction

Josephson M et al, Transplantation 2006;81:74
Polyoma Virus (BK Virus)

- Monitoring
  - Urine or serum viral load (PCR), biopsy
  - Role still to be determined
- Management (no clear guidelines)
  - 1st line therapy: modify immunosuppression
  - Antiviral therapy
  - Miscellaneous
Modification of immunosuppression

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

PVAN, polyomavirus-associated nephropathy; CsA, cyclosporine A; MMF, mycophenolate mofetil.

**B-III:** Moderate evidence to support a recommendation based on clinical experience, descriptive studies, or reports of expert committees.

**C-III:** Poor evidence to support a recommendation based on clinical experience, descriptive studies, or reports of expert committees.
BLOOD BK-PCR MONTHS 1, 2, 3, 6 and 12, and UPON RENAL DYSFUNCTION

BLOOD BK-PCR

Increased serum creatinine
  → Biopsy
    → Rejection + BKVN
      1) Rx rejection with IVIG & consider 2–6
    2) Decrease immunosuppression
    3) Quinolone or cidofovir?
    4) Leflunomide to replace the antimetabolite?
    5) Monitor creatinine
    6) Monitor BK q 2 weeks until clear
  → BKVN alone
  → No BKVN

Normal serum creatinine
  → Decrease Immunosuppression and Monitor q 2 weeks until clear
  → Increased creatinine
  → Normal creatinine
  → Repeat biopsy
  → Follow-up

Polyomavirus Nephropathy
Take-home points

• DNA virus causing interstitial nephritis (nephropathy) after renal transplant

• Related to over-immunosuppression, reactivation of virus latent in transplanted kidney

• Usually leads to inexorable graft loss unless identified early

• MONITOR! MONITOR! MONITOR!
PCP (PJP?)

- *Pneumocystis jiroveci* causing pulmonary infection
  - Insidious onset
- High mortality rates
- Effective prophylaxis
  - *SMX/TMP*, pentamidine, or dapsone
Hepatitis C (HCV)

- Overall incidence increasing in the U.S
  - >30% of liver transplant pts are HCV +
- Recurrence in virtually all patients
- Risks
- Primary treatment is prevention
  - Steroid sparing/free immunosuppression for liver transplant
- Treatment
  - Concern for increase acute rejection with Interferon alpha
Cancer after transplant

• Skin/lip most common – Majority of all malignancies
  – More squamous cell (250x higher vs general pop) vs. basal cell (10x higher vs. general pop)
• Anogenital- 2-3% of all malignancies
• Renal carcinomas- 0.5 -3.9% of malignancies
• PTLD- 1 -5% of malignancies
  – EBV with causative role
What is PTLD?

- **An EBV-related disease** - B cell proliferation induced by EBV infection

**Reactive Hyperplasia**
- Post-transplant infectious mononucleosis
- Plasma cell hyperplasia

**Neoplasia**
- Polymorphic B cell hyperplasia
- Polymorphic lymphoma
EBV and PTLD

- 95% of population is EBV IgG+
- ~5% of KTx recipients are EBV- recipients of EBV+ kidneys
- PTLD occurs in ~1% overall
- 80% of PTLD occurs in EBV- recipients
- Incidence of PTLD in EBV- recipients is as high as 20%!

1000 recipients:

50 EBV+/- 950 EBV+/+

10 cases PTLD

8 PTLD 2 PTLD
EBV+/- EBV++
Risk for PTLD/Lymphoma is increased with ATG (Thymoglobulin) and OKT3

Transplantation 2005; 80(9):1233-43.
Treatment of PTLD: Immunosuppression reduction

- **Limited Disease:**
  - 25% reduction
    - if triple therapy, may D/C antiproliferative (i.e. mycophenolate) medication

- **Extensive Disease:**
  - Critically ill:
    - Stop all immunosuppression
    - Prednisone at 7.5-10 mg/d
    - Frequent biopsies, avoid rejection
    - Bolus with steroids prn rejection
  - Not critically ill:
    - D/C antiproliferative agent,
    - decrease calcineurin inhibitor by 50%,
    - maintain prednisone at 7.5-10 mg/d
PTLD: Rituximab or Chemotherapy?

- Of 117 patients treated for PTLD from 1996-2005 at a single center, 35 failed immunosuppression dose reduction and survived to receive rituximab, chemotherapy, or both:
  - 22 received rituximab:
    - 13 had complete response (59%), those without response received chemotherapy
    - Median survival 31 months
  - 23 received chemotherapy:
    - 13 had complete response (57%)
    - Median survival 42 months
    - 26% died due to toxicities of therapy

Elstrom R et al, Am J Transplantation 2006; 6: 569
PTLD: Take-home points

• EBV related lymphoma

• Anti-Thymocyte Globulin (ATG) and OTK3 use increase risk

• Know your patient’s EBV serostatus, consider more rapid IS taper in EBV+/- recipients

• If PTLD develops:
  – Reduction in immunosuppression is 1\textsuperscript{st} line
  – Rituximab +/- chemotherapy next step
Candidiasis

- Most common fungal infection
- Seeing rise of resistant species
  - *C. krusei* & *C. glabrata*

Pathogenesis

- Disruption of normal defense mechanisms
  - IV lines and broad spectrum antibiotic use
Aspergillosis

• Grows in soil and decaying organic material
• Acquired via inhalation
• Case clusters reported in oncology and transplant units
  – Mainly invasive aspergillosis
Miscellaneous Fungal Infections

- Cryptococcosis
- Endemic Infections
  - Prophylaxis often utilized
- Zygomycosis
Infectious Complications

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

**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:
  - Polymavirus 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 polymavirus infection (PML)
  - Skin cancer, lymphoma (PTLD)

Dynamic assessment of risk of infection
Prophylactic Therapy Summary

- CMV
  - 3 - 12 months valgancyclovir or gancyclovir
- PCP
  - 6 – 12 months TMP/SMX
- Candidasis
  - 1 to 3 months (agents vary)
- Fungal infections
  - 6 – 12 months fluconazole for endemic fungus
  - Lifelong itraconazole in lung transplant