Infections in Adult Solid Organ Transplantation

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Focus

- Donor and Recipient Screening and Risk assessment
- Review of the induction and maintenance IS agents and infections associated with them
- Review standardization of the use of PCP and CMV prophylaxis
- Focus on CMV, EBV and Polyoma BK virus
- Emerging infections such as CDAD, MTB, arboviruses and parasites will be discussed separately

The “BMT Engraftment” Model
Donor Screening

- Epidemiologic and risk factor assessment
- Chart review
  - Reason for hospitalization and cause of present illness
  - If active or past infection, assessment for appropriate antibiotic management and course
  - Other possible infections? (e.g., encephalitis, sepsis/blood stream infection)
- Serologic testing, Routine
- Serologic testing, tailored
- Microbiologic review: blood, urine and respiratory cultures
- CXR and other pertinent radiography
- Per Center and OPO protocols, NAT for blood borne pathogens

Donor Screening

- United Network of Organ Sharing
  - CMV IgG
  - EBV - VCA or EBNA antibody test may be performed if the recipient is EBV seronegative
  - HIV 1,2 EIA
  - HTLV 1,2 EIA
  - HBsAg, HbcAB, HBSAb
  - HCV EIA
  - RPR
  - Tuberculosis
    - Strongyloides for donors from endemic areas
    - Trypanosoma cruzi for donors from endemic areas
    - West Nile for endemic areas
  - Toxoplasmosis
  - Encouraged OPO specific policies re: NAT for HIV/HCV/HBV

HTLV 1-2 screening recently removed from UNOS screening criteria

Donor Related Infections

Nucleic Acid Amplification Technology and associated “windows” (NAT)

<table>
<thead>
<tr>
<th>Virus</th>
<th>Serology Window (median, days)</th>
<th>NAT Window (median, estimated, days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV</td>
<td>60</td>
<td>25</td>
</tr>
<tr>
<td>HCV</td>
<td>70</td>
<td>8-10</td>
</tr>
<tr>
<td>HIV</td>
<td>23</td>
<td>13</td>
</tr>
</tbody>
</table>
Recipient Screening

Recipient Checklist

- Epidemiologic history and screening
  - Work, Travel/residence, hobbies, pets, military, healthcare employment, incarceration, family members incarcerated or in military and where stationed
- Vaccine history (some centers confirm with serologies)
  - Standard serologies including: RPR or VDRL, HIV, HBV (HBsAg, HBsAb, HBeAb), HCV, EBV and CMV. Some include Toxoplasma, VZV, HSV 1 and 2
  - PPD or equivalent, and if prior reactive or evidence of LTBI, treatment history
- Known infections (e.g., MRSA, ESBL Enterobacteriaceae, C. difficile disease, LTBI and treatment course)
- Assessment for latent infections (e.g., Histoplasma, Coccidioides, Strongyloides, LTBI)
- Possible Infections (e.g., LCMV)
- NB: when possible, include NAT or Ag testing for pathogen if susceptibility in some cases, particularly BMT and heme malignancies, Ab screening will not be reliable.

Recipient Infection Risk Assessment:

- What’s modifiable and what’s not
  
  **High Risk, Peritransplant:**
  - Induction therapy with lymphocyte depletion
  - High-dose pulse steroids
  - Pheresis
  - Risk for rejection (ABO mismatch, high PRA, etc)
  - Active infection in either donor or recipient

  **High Risk, Technical:**
  - Anastomotic leak
  - Bleeding
  - Return to OR
  - Wound site infection or dehiscence
  - Prolonged intubation
  - Prolonged use of invasive catheters

  **High Risk, Post Transplant:**
  - Graft dysfunction or DGF
  - Latent infection in Donor or Recipient
  - Acute or chronic rejection

  **Low(er) Risk:**
  - Good HLA match
  - Good or immediate graft function
  - Short OR time
  - Technically easy transplant
  - Good or immediate graft function

- Directed to latent infections, e.g., LTBI, Histoplasmosis, Coccidioides

- Based upon Transplant Unit, ICU and hospital antibiograms

- Preliminary risk assessment of patient and need for any adjustments (e.g., cefazolin won’t be good for pt with recent ESBL infection)

- Directed therapy to latent infections, e.g., LTBI, Coccidioides, Histoplasmosis
Immunosuppression

**Goal:** to prevent rejection events while minimizing collateral damage
- CD = nonopportunistic and opportunistic infections and malignancies, and long term secondary drug effects

**Achieved by:**
- **Induction Immunosuppression**
  - Immediately prevents any HLA or alloantigen processing
  - Minimizes exposure to calcineurin inhibitors and reduces the need for prolonged steroid management
  - Agents include:
    - Antilymphocyte Antibodies (eliminate target)
      - ATG, OKT3
    - IL-2 receptor blockade (eliminate signalling)
      - basiliximab and daclizumab
    - Block everything
      - alemtuzumab

- **Maintenance Immunosuppression**
  - Lower level IS that permits recovery of recipient immunity to a point
  - Targeted to minimize signal transduction, signal triggering, or cell cycling.

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**Induction Immunosuppression**

- Immediately eliminates or blocks T cell activation and antigen presentation/recognition
- Minimizes exposure to calcineurin inhibitors and reduces the need for prolonged steroid management

**Agents include:**
- Antilymphocyte Antibodies (eliminate target)
  - ATG, OKT3
- IL-2 receptor blockade (eliminate signalling)
  - basiliximab and daclizumab
- Block everything
  - alemtuzumab
Infectious Complications

**ATG:**
- Largely bacterial
  - Enterococcus
  - Staphylococcus
  - Acinetobacter
  - Proteus
  - Pseudomonas
- Enterobacteriaceae

**Viruses:**
- CMV: More on this later
- Herpes
- Adenovirus

**Fungal Infections:**
- IFI not increased

**OKT3**
- Rarely used due to markedly increased risks of:
  - Severe CMV infection, invasive fungal infections, and EBV associated PTLD
  - T1/2 effect markedly longer than ATG

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IL-2R associated infections

- Overall rates of bacterial, viral including CMV, and HCV reactivation, and fungal infections are not statistically different than that of placebo or other induction therapies if appropriate PCP and CMV ppx are used.
- Unlike OKT3, there was no increased risk for EBV-associated PTLD.

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Campath (alemtuzumab, Anti CD52)

- Humanized mouse monoclonal antibody directed against the CD52 surface antigen.
  - Mature and long-lived T cells,
  - B cells including plasma cells,
  - APC including monocytes, macrophages, and dendritic cells,
  - PMNs and NK Cells
- Mechanisms for lymphocyte depletion includes:
  - Complement fixation
  - ADCC
  - Growth inhibition as a result of crosslinking the CD52 target antigen.
- Duration of action may be as long as 3–12 months (dose dependent)
The doses of alemtuzumab in SOT induction are lower than what are used in hemato-malignancies. Complications have included:
- Pseudomonas sepsis
- Pulmonary and disseminated nocardiosis
- MTB reactivation with dissemination
- NTM infection (PNA, M. kansasii)

Infectious complications clearly dose related:
- Peleg et al, CID 2007:
  - Re-use of alemtuzumab in AR increased infectious complications minimum of 5 fold vs IS induction alone
  - Lung, multi-organ or repeat organ, small intestine were independent predictors of infectious complications

![Stylized Timeline of Potential Infections post solid organ transplantation](image)

**Antimicrobial Resistance in Primary Bacterial Isolates, BIDMC Transplant Unit 2002-2005**

<table>
<thead>
<tr>
<th>Organism</th>
<th>N</th>
<th>Antimicrobial</th>
<th>% Susceptible</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klebsiella</td>
<td>13</td>
<td>ceftriaxone</td>
<td>62 91 86</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>piperacillin</td>
<td>35 38 38</td>
<td>10 (3-38)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>gentamicin</td>
<td>35 38 38</td>
<td>15 (4-61)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pseudomonas</td>
<td>4</td>
<td>ceftriaxone</td>
<td>78 85 77 98</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>imipenem</td>
<td>82 91 91 78</td>
<td>0.8 (0.1-3.9)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td></td>
<td>gentamicin</td>
<td>82 91 91 78</td>
<td>0.9 (0.01-3.9)</td>
<td>ns</td>
</tr>
<tr>
<td>E coli</td>
<td>9</td>
<td>ceftriaxone</td>
<td>98 98 96 98</td>
<td>0.3 (0.1-2.4)</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td></td>
<td>levofloxacin</td>
<td>78 78 55 55</td>
<td>0.3 (0.1-2.4)</td>
<td>ns</td>
</tr>
<tr>
<td>Enterobacter</td>
<td>6</td>
<td>ceftriaxone</td>
<td>81 81 100</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>gentamicin</td>
<td>33 33 33</td>
<td>9 (1.1-100)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>S. aureus</td>
<td>1</td>
<td>oxacillin</td>
<td>43 43 43 43</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>vancomycin</td>
<td>33 33 33 33</td>
<td>5.3 (2.5-11.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Enterococcus</td>
<td>3</td>
<td>ceftriaxone</td>
<td>73 73 73</td>
<td>ns</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>levofloxacin</td>
<td>33 33 33</td>
<td>0.9 (0.2-4)</td>
<td>ns</td>
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<td></td>
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<td>vancomycin</td>
<td>33 33 33</td>
<td>5.3 (2.5-11.3)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
## Preliminary univariate risk factor analysis for invasive fungal infection in OLT, 2002-2005

<table>
<thead>
<tr>
<th>Variable</th>
<th>N (%) N=40</th>
<th>Yes (%) N=13</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>54</td>
<td>5</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>OLT</td>
<td>37 (92)</td>
<td>10 (77)</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>Roux-en Y anastamoses</td>
<td>4 (10)</td>
<td>5 (38)</td>
<td>5.6 (1-34)</td>
<td>0.02</td>
</tr>
<tr>
<td>Median Warm ischemic time (minutes)</td>
<td>55</td>
<td>2</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>Median Cold ischemic time (minutes)</td>
<td>452</td>
<td>469</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Blood Products &gt;40 Units</td>
<td>7 (18)</td>
<td>9 (69)</td>
<td>10.3 (2-57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Colonization Pre-Transplant</td>
<td>2 (5)</td>
<td>7 (54)</td>
<td>22 (3-244)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Repeat OR &lt;5 days not including re-transplant</td>
<td>2 (5)</td>
<td>7 (54)</td>
<td>22 (3-244)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Repeat Transplant</td>
<td>1 (2.5)</td>
<td>3 (23)</td>
<td>11.7 (0.8-92)</td>
<td>0.002</td>
</tr>
<tr>
<td>Vascular complication</td>
<td>3 (7.5)</td>
<td>7 (54)</td>
<td>14.4 (1.3-112)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Vascular complications included HAT/HAS, portal vein thrombosis or anastomotic repair, and could not be included in the model.

## Preliminary multivariate logistic regression analysis for risk factors associated with IFI*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-transplant colonization</td>
<td>104.3 (9.1250)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Return to OR &lt;5 days excluding re-transplant</td>
<td>22 (1.3-381)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*Vascular complications included HAT/HAS, portal vein thrombosis or anastomotic repair, and could not be included in the model.
Modifiable risk and effect of antifungal prophylaxis in a priori defined high risk OLT pts who developed IFI by day 100.

Hadley et al. Transplant Infect Dis 2009;11:40-8

Maintenance Immunosuppression

- 1 from:
  - Calcineurin Inhibitors (CNI)
    - cyclosporin or tacrolimus or
  - Rapamycin
    - (conversion from CNI, never used initially due to inhibition of endothelial cell proliferation)
  - PLUS:
- 1 from: antimetabolite
  - mycophenylate mofetil or azathioprin
- Sometimes, low dose prednisone
  - associated with race/ethnicity

Calcineurin inhibition

- Cyclosporin (Neoral®, Sandimmune®, Gengraf®)
- Tacrolimus (FK506, Prograf®)
- The mechanisms of calcineurine inhibitors (CNIs) converge at the inhibition of calcineurin
  - (a signal transduction pathway that leads to NFκB activation and upregulation of IL-2 production)
  - This inhibition ultimately inhibits the production and secretion of IL-2.
  - The interaction between IL-2 and the IL-2 receptor is crucial in the activation and differentiation of B and T cells.
  - Therefore, halting the rejection process at this step is highly effective at combating rejection.
Antimetabolites

- **Mycophenolate Mofetil** -
  - Inhibits activated lymphocytes preventing cell cycling.
  - Uncertain therapeutic window.

- **Azathioprine** -
  - Precursor to 5 Mercaptopurine.
  - This ultimately prevents mitosis and proliferation of rapidly dividing cells, such as activated B and T lymphocytes.
  - Blocks most T-cell functions.
  - Inhibits primary antibody synthesis.
  - Little effect on established immune responses, and is therefore effective only in the prevention (not treatment) of acute rejection.
CMV

- Association with ATG well known and is the result of TNFα release at the time of fever with ATG infusion. Cellular NFkB binds to a promoter region of the CMV immediate early antigen gene.
- Other factors associated with CMV activation include:
  - Donor/recipient status
  - Degree of T lymphocyte depletion (both CD4 and CD8, and ratio as TH-2 responses far less protective than TH-1/TH-2)
  - Type and dosage of lymphocyte depleting agents, including re-treatment for AR
  - Prolonged high-dose maintenance agent like MMF, AZA, pred if used
  - CMV prophylaxis used or not


Pathways for CMV Reactivation From Latency

- Up regulation of TNF-alpha, IL-2, and proinflammatory cytokines
- Activation of leukocytes, endothelial cells, smooth muscle cells, and dendritic cells
- Despite use of IL-2 and cell cycle inhibiting agents, the CMV activation overcomes maintenance IS effects, and graft alloantigens becoming targets, resulting in acute rejection
- The Converse is also true: AR events even prior to IS intervention can result in CMV reactivation


Mechanisms by Which CMV May Harm the Allograft: Cellular Effects

- Endothelial cells infected with CMV ⇒ neutrophil and CTL responses
- Increase of MHC antigens
  - Sequence homology and immunologic cross-reactivity between CMV IE antigen and HLA-DRβ chain
  - CMV-infected cells produce glycoprotein homologous to MHC class I antigens
- Upregulation of proinflammatory adhesion molecules
- CMV ⇒ autoantibodies; humoral rejection

Incidence of Graft Failure in Hepatitis C Liver Recipients Based on CMV Infection

**Infection Status Graft Failure**

<table>
<thead>
<tr>
<th>CMV (negative)</th>
<th>13/18 (19%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV (positive)</td>
<td>13/25 (52%)</td>
</tr>
</tbody>
</table>

\[ P = 0.02 \]

Risk of CMV Disease in SOT Recipients

<table>
<thead>
<tr>
<th>Serologic Status</th>
<th>Incidence of Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor + Recipient -</td>
<td>CyA or FK, pred, MMF or Aza</td>
</tr>
<tr>
<td>Donor ? Recipient +</td>
<td>CyA or FK, pred, MMF or Aza</td>
</tr>
<tr>
<td>Donor ? Recipient +</td>
<td>Induction antilymphocyte Ab, followed by standard 3 drugs</td>
</tr>
<tr>
<td>Donor ? Recipient +</td>
<td>Antirejection antilymphocyte Ab, followed by standard 3 drugs</td>
</tr>
<tr>
<td>Donor - Recipient -</td>
<td>Any</td>
</tr>
</tbody>
</table>

CyA = cyclosporine; FK = tacrolimus; pred = prednisone; MMF = mycophenolate mofetil; Aza = azathioprine; ab = antibody.

*Provided "pedigreed" leukopheresed blood products used.

Slifkin et al. Drugs 2004;64:2753-92

Rate of CMV Disease Despite Antiviral Prophylaxis in High Risk recipients (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>

<table>
<thead>
<tr>
<th>Hepatic Transplants</th>
<th>Placebo</th>
<th>Ganciclovir (po)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis (3 mo)</td>
<td>44%</td>
<td>5%</td>
</tr>
<tr>
<td>Postprophylaxis (6 mo)</td>
<td>44%</td>
<td>15%</td>
</tr>
</tbody>
</table>


Stylized Timeline of Potential Infections post solid organ transplantation

Adopted from Fishman JA, NEJM 357;25:2007

Modifications to prevent OIs

- **TMP/SMX:**
  - Well proven for PJP/PCP ppx;
  - May limit Nocardia complications such as dissemination;
  - Very useful in heart/heart-lung transplants and preventing toxoplasma reactivation;
  - Other bacterial infections may be prevented (e.g., Listeria, staphylococci, GN UTIs)

- **Fluconazole:**
  - Colonization and invasive rates statistically reduced in fluconazole treated OLT recipients;
  - Useful for secondary prophylaxis for endemic mycoses*
  - Primary agent for Coccidioides immitis and Cryptococcus neoformans; secondary agent for Histoplasma capsulatum

Modalities to Prevent Viral Infections in SOT

<table>
<thead>
<tr>
<th>Modality</th>
<th>CHV</th>
<th>HBV</th>
<th>HAV</th>
<th>VZV</th>
<th>EBV</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoidance</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>HCV, HBV, HAV</td>
</tr>
<tr>
<td>Vaccine</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>HBV, HAV</td>
</tr>
<tr>
<td>Passive Immunity</td>
<td>CHV</td>
<td></td>
<td></td>
<td>VZV</td>
<td></td>
<td>HAV, HBV</td>
</tr>
<tr>
<td>Immune Modulation</td>
<td></td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td>IFN for HBV and HAV</td>
</tr>
<tr>
<td>Antiviral agents</td>
<td>GCV, ACV, VGCV</td>
<td>ACV, WACV, TACV, VGCV</td>
<td>ACV, VACV, TACV, VGCV</td>
<td>VGCV</td>
<td>3TC, FTC, TDF, ADF, ECV</td>
<td></td>
</tr>
</tbody>
</table>
DEFINITIONS OF PROPHYLAXIS AND PRE-EMPTIVE THERAPY

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Definition</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis</td>
<td>Administration of an agent prior to infection or disease</td>
<td>Ease of administration to defined individuals</td>
<td>Low risk persons exposed to unnecessary agent with known toxicities. Prolonged or incorrect dosing may lead to emergence of resistance.</td>
</tr>
<tr>
<td>Pre-Emptive</td>
<td>Highly directed therapy to persons who exhibit positive marker (pDNA PCR, bDNA PCR, antigenemia)</td>
<td>Minimizes unnecessary exposure to drug.</td>
<td>Requires validated highly sensitive surveillance at biologically reasonable intervals.</td>
</tr>
</tbody>
</table>

Efficacy and Safety of Valganciclovir vs. Oral Ganciclovir for Prevention of Cytomegalovirus Disease in Solid Organ Transplant Recipients

Table 1: Summary of cytomegalovirus CMV disease up to 6 and 12 months post transplant, in the first 100 patients as selected by the CMV Prophylaxis Committee (data are cumulative). Events up to 6 months post transplant include the events up to 6 months. CMV disease risk in transplant recipients.

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage of Patients (n: 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV disease</td>
<td></td>
</tr>
<tr>
<td>CMV syndrome</td>
<td>0.6% (6)</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>4% (14)</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>1% (1)</td>
</tr>
<tr>
<td>Other</td>
<td>1% (1)</td>
</tr>
<tr>
<td>Histocompatibility/match</td>
<td>4% (16)</td>
</tr>
</tbody>
</table>

Table 2: Summary of cytomegalovirus CMV disease as the first 100 patients post transplant (as defined by 100 patients).

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage of Patients (n: 100)</th>
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<tbody>
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</tr>
<tr>
<td>Prophylaxis</td>
<td>1% (1)</td>
</tr>
<tr>
<td>Other</td>
<td>1% (1)</td>
</tr>
</tbody>
</table>

Table 3: Summary of cytomegalovirus CMV disease as the first 100 patients post transplant (as defined by 100 patients).

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</tr>
<tr>
<td>Immunosuppression</td>
<td>4% (14)</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>1% (1)</td>
</tr>
<tr>
<td>Other</td>
<td>1% (1)</td>
</tr>
</tbody>
</table>
Conclusions

By understanding the pharmacology, epidemiology and associated risk factors associated with infectious complications post organ transplant, we can modify those outcomes.

- Careful pre-transplant screening of the recipient and donor
- Appropriate antimicrobial prophylaxis
- Remembering to “restart” the immunologic clock with Acute Rejection therapies

More slides

- More Slides
CMV

Effects of CMV: Overview

- Infectious
- Graft rejection
- Antilymphocyte antibodies
- Nephritis, hepatitis, carditis, pneumonitis, pancreatitis, colitis, retinitis, cytopenias
- Atherosclerosis, bronchiolitis obliterans, vanishing bile-duct syndrome

Latent CMV infection
Active CMV infection
(viremia and invasion)

EBV-associated PTLD early

Systemic immune suppression

Cellular effects: antigen and cytokine expression

Acute Acute Chronic
Opportunistic infection, IFI

Survival analyses demonstrating statistical non-inferiority between vGCV and oral GCV ppx arms by end-point defined and ITT analyses
While overall, the results showed noninferiority of valGCV to GCV with regards to CMV disease, there was overall superiority regarding acute rejection rates. Though the investigators did not show the CMV rates by organ transplanted, the clear superiority was in the KT recipients receiving valGCV. There was a suggestion that GCV was superior in OLT.


EBV

- EBV induced post-transplant lymphoproliferative disorders (PTLD):
  - Heterogenous group of lymphoproliferative disease associated with EBV infections in solid and liquid organ transplant recipients.
- Allogeneic BMT/Stem Cell Transplant
  - EBV transformation of donor T cells (occasionally T cells)
  - T-cell depleted or antigen-mismatch transplants (MUD), cord-blood allogeneic HSCT are primary risk factors.
  - NB- this is highly correlated to the type of marrow conditioning regimen applied at the time of transplantation.

- Solid Organ Transplant
  - EBV transformation of recipient cells in majority of cases;
  - EBV transformation of donor lymphocytes within the donor organ has been described
  - ALAs used at induction, with repeat exposure due to 1) retransplantation (new organ, second organ); 2) AR that is steroid unresponsive.

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**Incidence**

- Pediatric population
  - 3-4% (OLT with cyclosporin)
  - 6-13% (tacrolimus)
  - 14-27% (OKT3 and prednisone resistant rejection)
  - Mortality: 10-20%

- Adult population
  - 0.8-3% (OLT with cyclosporin)
  - 5-10% (thoracic organ transplant)
  - >20% (steroid resistant rejection)
  - Mortality: 50-80%

Ho, et al. Transplantation 1988;45:719

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**Incidence of EBV+ and EBV- PTLD by Organ Transplanted**

<table>
<thead>
<tr>
<th>Organ</th>
<th>Overall % (n)</th>
<th>Report %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>1.3 (7/177)</td>
<td>0.2-4.5</td>
</tr>
<tr>
<td>Pediatric</td>
<td>12 (12/100)</td>
<td>0-6</td>
</tr>
<tr>
<td>Liver</td>
<td>2.1 (6/295)</td>
<td>2.1-7.1</td>
</tr>
<tr>
<td>Pediatric</td>
<td>6 (6/100)</td>
<td>1.9-2.2</td>
</tr>
<tr>
<td>Heart</td>
<td>2.5 (21/380)</td>
<td>1.9-2.2</td>
</tr>
<tr>
<td>Pancreas-kidney</td>
<td>6.4 (6/91)</td>
<td>1.9-9.1</td>
</tr>
<tr>
<td>Liver Heart</td>
<td>6.3 (6/97)</td>
<td>1.8-3.9</td>
</tr>
<tr>
<td>Pediatric</td>
<td>14 (14/100)</td>
<td>1.8-3.9</td>
</tr>
<tr>
<td>Heart</td>
<td>9.6 (9/94)</td>
<td>1.8-3.9</td>
</tr>
<tr>
<td>Pancreas-kidney</td>
<td>4.5 (4/91)</td>
<td>1.9-9.1</td>
</tr>
<tr>
<td>Heart</td>
<td>5.3 (5/97)</td>
<td>1.8-3.9</td>
</tr>
</tbody>
</table>

EBV - Epstein-Barr virus; NA - not applicable; R+ - recipient positive; R- - recipient negative.

Incidence of PTLD in EBV+/- Recipients by risk factors


<table>
<thead>
<tr>
<th>Human Polyomavirus</th>
<th>Date identified</th>
<th>Major Cell type infected</th>
<th>Associated disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>BKV</td>
<td>1971 (Gardner et al)</td>
<td>Kidney epithelial and uroepithelial cells</td>
<td>Hemorrhagic cystitis, BK nephropathy, encephalitis</td>
</tr>
<tr>
<td>JCV</td>
<td>1971 (Padgett et al)</td>
<td>Kidney epithelium, B cells, oligodendrocytes</td>
<td>PML</td>
</tr>
<tr>
<td>KI</td>
<td>2007 (Shander et al)</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>WU</td>
<td>2007 (Gaynor et al)</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>MCV</td>
<td>2008 (Feng et al)</td>
<td>Merkel Cells</td>
<td>Merkel Cell Carcinoma</td>
</tr>
</tbody>
</table>
BK complications

- BK viruria and viremia is reported in up to 80% of renal transplant recipients with 10% progressing to BKN with graft loss occurring in up to 90% of these cases
  - Clearly more strongly associated with BK viremia as most viruria is asymptomatic shedding
  - Pathology is proximal tubular necrosis and denudation of the basement membrane directly associated with lytic phase of viral replication
  - Pathognomonic cells shed in urine are the Decoy Cells (uroepithelium with viral inclusions)

- No single risk factor for development of BKN
  - Overall degree of IS and not the specific agents employed is a key factor, though it’s clear that BKN rarely occurs in other non-renal solid organ transplants or in allogeneic stem cell transplants
    - In these cases, only asymptomatic viruria occurs or hemorrhagic cystitis
  - In renal transplantation, other factors appear to be donor seropositive, male sex, older age (>55), specific HLA loci and HLA mismatches, and use of AL Ab antirejection therapy.
Treatment

- Primary treatment of BKN is decreasing immunosuppression
- Alternatives is to replace MMF with lefluonomide
- Antiviral therapy with cidofovir is controversial but may be useful
- Some weak anecdotal data suggesting quinolones may play a roll in preventing or decreasing severity of BKN in viremic pts

HBV

- **HBSAg+**
  - expressing viral surface protein and active replication
- **HBCAb+**
  - indicates prior infection; may be false positive (up to 10% of pts with ESRD can have weakly positive HBCAb EIA); in case of lost HBSAb, only useful for marker of prior infection; NOT protective
- **HBSAb+**
  - Minimum EIA titer of 10IU/mL to trigger "positive" result in labs; strongly neutralizing
- In pts who had prior HBV infection (i.e., HBSAb+/CaB+ OR HBSAb-/CaB+), though they do not have circulating or replicating virus, they have nonreplicating HBVcccDNA dormant in the hepatocyte nucleus. This serves as a reservoir for potential future reactivation within the recipient. Must also be considered in OLT if the DONOR is HBCAb+
Agents associated with HBV reactivation

- Pulse steroid exposure
- Rituximab therapy
- Antilymphocyte antibodies
- IL2R antibodies
- alemtuzumab
- Pheresis
- Acute rejection therapy


Table 1. Etiologic Classification of Acute Flares in Chronic Hepatitis B

<table>
<thead>
<tr>
<th>Etiologic Classification</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Autoimmune hepatitis</td>
<td>Autoimmune hepatitis due to antinuclear/antiviral antibodies</td>
</tr>
<tr>
<td>Drug-induced hepatitis</td>
<td>Drug-induced hepatitis due to medications</td>
</tr>
<tr>
<td>Acute viral hepatitis</td>
<td>Acute viral hepatitis due to HBV hepatitis</td>
</tr>
<tr>
<td>Acute alcoholic hepatitis</td>
<td>Acute alcoholic hepatitis due to alcohol intake</td>
</tr>
<tr>
<td>Acute ischemic hepatitis</td>
<td>Acute ischemic hepatitis due to liver failure</td>
</tr>
<tr>
<td>Acute reactivation</td>
<td>Acute reactivation due to HBV reactivation</td>
</tr>
<tr>
<td>Acute rejection</td>
<td>Acute rejection due to immune reconstitution therapy</td>
</tr>
</tbody>
</table>

Steroid Dependent Promotor Region

PheS1 e PheS2
HBV recurrence post orthotopic liver transplantation with and without passive immunoprophylaxis

359 patients evaluated from 372 consecutive patients expressing HBSAg transplanted in 17 centers from 1977-1990.
Short Term = 2 months HBIG
Long Term = 6 months HBIG


Antiviral Agents

- Various studies are assessing the utility of lamivudine vs adefovir vs entecavir for secondary ppx in HBV D+/R- or R+. Much is center specific; at present, standard of care is use of HBIG.

Summary and Conclusions

- Organ and recipient survival as well as acute rejection rates have markedly improved with more targeted immunosuppression approaches
- Post-transplant recipient infections are the result of both recipient and donor factors
Modifiable risk factors include:

- Good pre-transplant screening of both the donor and the recipient
- Use or modified use of antilymphocyte depleting antibodies induction
- Minimizing steroid exposure
- Protocolizing OI prophylaxis based upon Donor and Recipient serologic history and automatically reinitiating in cases of AR

Nonmodifiable risk factors are largely technical and include:

- Time of transplant surgical complications
- Post-surgical complications such as anastamotic dehiscence, post-surgical bleeding in high-risk patients
- ABO or high-grade HLA mismatches in the cases of Priority 1 transplants

It is a must for the Transplant ID specialist to understand the immunologic alterations associated with IS and to be available for ad hoc discussions at time of donor assessment.