Topics To Be Discussed

- How are we doing in transplantation?
- Review basic precepts of transplant infections
- Discuss some classic transplant pathogens: CMV, EBV, fungal diseases, pneumocystis, TB
- Emerging transplant problems: polyomaviruses, RSV, respiratory viruses, arenaviruses
- Avoidance of infection
### Graft and Patient Survival After Transplantation by Organ

<table>
<thead>
<tr>
<th>Type</th>
<th>Graft Survival (%)</th>
<th>Patient Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 year</td>
<td>3 year</td>
</tr>
<tr>
<td>Renal-LD</td>
<td>96</td>
<td>90</td>
</tr>
<tr>
<td>Renal-Cad</td>
<td>91</td>
<td>80</td>
</tr>
<tr>
<td>Pancreas</td>
<td>76</td>
<td>60</td>
</tr>
<tr>
<td>Heart</td>
<td>88</td>
<td>81</td>
</tr>
<tr>
<td>Liver</td>
<td>84</td>
<td>74</td>
</tr>
<tr>
<td>Lung</td>
<td>82</td>
<td>64</td>
</tr>
<tr>
<td>Heart-Lung</td>
<td>81</td>
<td>62</td>
</tr>
</tbody>
</table>

Data from SRTR 2009 Annual Report
Decreasing Infectious Mortality in Subsequent Cardiac Transplant Cohorts 1980-1990
Lack of Change in Infectious Mortality after Cardiac Transplantation: 1990-2000

CTRD: 1990 - 1999, n=7,290

Date of Transplant

% of Patients Who Died from Specific Cause Within 3 Years

- Infection
- Graft Vasculopathy
- Rejection
- Early Graft Failure
- Malignancy
Infection Related Mortality in Lung Transplant Recipients

Proportion of All Deaths Related to Cause

VUMC Data
Basic Precepts of Transplant Infections

- Infections occur on a time scale

- Type and frequency of infection vary with transplant type: lung > liver > heart > kidney

- More surgery → more infection

- More immunosuppression → more infection

- Beware of donor as a source of infection especially early post-transplant

- Transplantation does not protect from infections “normal” people get
Time Scale of Infection after Transplantation

Types of Infections vary depending on time post-transplant:

- 0-30 days: mostly "surgical" infections, common bacteria, Candida, HSV
- 1-6 months: opportunistic pathogens, CMV, Pneumocystis, Nocardia, Aspergillus
- 6 months onward: common community infections, occasional opportunists, endemic fungi (histo, crypto)
### Frequency and Severity of Infections by Organ

<table>
<thead>
<tr>
<th>Type</th>
<th>N</th>
<th>Inf /Pt.</th>
<th>CMV</th>
<th>Bacteremia</th>
<th>Fungal</th>
<th>Inf. Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal</td>
<td>64</td>
<td>0.98</td>
<td>8%</td>
<td>5%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Heart</td>
<td>119</td>
<td>1.36</td>
<td>16%</td>
<td>13%</td>
<td>8%</td>
<td>15%</td>
</tr>
<tr>
<td>Liver</td>
<td>101</td>
<td>1.86</td>
<td>22%</td>
<td>16%</td>
<td>16%</td>
<td>23%</td>
</tr>
<tr>
<td>H-Lung</td>
<td>31</td>
<td>3.19</td>
<td>39%</td>
<td>19%</td>
<td>23%</td>
<td>45%</td>
</tr>
</tbody>
</table>

Dummer JS, PPID, 2000, Churchill Livingstone, based on data from early 1980’s in Pittsburgh
Partial List of Organisms Transmitted by Transplantation

- **Viruses:** CMV and other herpesviruses, HIV, hepatitis A, B C & D, HTLV-1, WNV, Rabies, LCMV

- **Fungi:** Histoplasma, Coccidioides, Cryptococcus

- **Protozoa:** Toxoplasma, malaria, *T. cruzii*

- **Bacteria:** TB, nosocomial pneumonia agents (lung), urinary bacteria (kidney), bacteremic donor

- **Prions:** Creutzfeld-Jakob disease (cornea)

Infectious Episodes Related to Total Time Spent in the Operating Room

![Bar chart showing the number of infection episodes per patient across different total operative time categories.](chart.png)

- **5-10 hours**: n=29
- **10-15 hours**: n=42
- **15-20 hours**: n=15
- **20-25 hours**: n=5
- **>25 hours**: n=10

**Total operative time in hours**

**Infection episodes per patient**
Immunosuppression and Infection
- A Summary

- No good marker is available for state of immunosuppression (unlike CD4 in HIV)
- “Net state of immunosuppression” must be estimated based on clinical status, doses or levels of drugs, and recent treatment of rejection
- Treatment of rejection increases clinical infection rates
- Patients are treated with a cocktail of oral drugs with different modes of action; some IV drugs are also used either for treatment of rejection or induction early post-transplant

Dummer JS, PPID, 2000; Halloran PF NEJM 2004;351:2715
Immunosuppression and Infection

- Infections increase with increased intensity of immunosuppression

- Two major immunosuppressive drugs introduced since 1980, cyclosporine and tacrolimus, have similar infectious risk but are associated with less infection than the earlier regimen of azathioprine/steroids

- Two cell cycle inhibiting agents, azathioprine and mycophenylate mofetil, have similar infectious risk

- Risk of post transplant malignancy and CMV may be reduced with rapamycin

Dummer JS, PPID, 2000
## Antibody Therapy and Infection

<table>
<thead>
<tr>
<th>Antithymocyte Globulin</th>
<th>Increased risk of CMV, PTLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabbit</td>
<td>Infection risk not significantly increased</td>
</tr>
<tr>
<td>Equine</td>
<td>HBV reactivation</td>
</tr>
</tbody>
</table>

| Anti-CD25 (IL-2 receptor) antibodies | Increased risk of CMV, Pneumocystis jirovecii pneumonia, invasive fungal infections, immunosuppression effects can last up to 12 months |
| Basiliximab (Simulect®)             | |

<table>
<thead>
<tr>
<th>Anti-CD20 antibody</th>
<th>Rituximab (Rituxan®)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased risk of CMV, Pneumocystis jirovecii pneumonia, invasive fungal infections, immunosuppression effects can last up to 12 months</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anti-CD52 antibody</th>
<th>Alemtuzumab (Campath®)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased risk of CMV, Pneumocystis jirovecii pneumonia, invasive fungal infections, immunosuppression effects can last up to 12 months</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Herpesvirus Infections after Transplantation

- Up to 35% of patients develop oral or genital herpes simplex infection in the first 2-3 weeks after transplantation; rare invasive or primary infections may be fatal
- Herpes zoster or shingles occurs in up to 1/3 of transplant recipients. Chicken pox can be fatal
- Epstein-Barr virus is associated with lymphoma after transplantation. Risk is 0.3-4%, may be 10 times higher with primary infection
- Human herpes virus 8 associated with Kaposi’s sarcoma after transplantation
- Cytomegalovirus has been the single most important pathogen in transplant recipients
Labial Herpes
Herpes Simplex Esophagitis
Herpes Simplex: Donor Transmitted Disease
Cytomegalovirus and Transplantation

- At one time CMV was the most important serious infection after transplantation
- Now largely controlled by antivirals
- Usually occurs 30-90 days after transplantation
- Manifestations: Fever most common, but sometimes invasive infection in bowel, liver, lung or retina
- Risk factors for disease are primary infection (usually donor derived), level of immunosuppression, organ transplanted (lung)
- Diagnosis used to be by viral culture, now most often by blood antigenemia or quant. PCR
- Treatment: ganciclovir, foscarnet
Infection and Morbidity due to CMV in Different Transplant Groups

Data collected in Pittsburgh before the use of antiviral medications
# Manifestations of CMV Disease Following Cardiac Transplantation

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>No. of Patients</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever ( &gt; 38^\circ )</td>
<td>17</td>
<td>100%</td>
</tr>
<tr>
<td>Atypical Lymphs ( &gt; 3% )</td>
<td>15</td>
<td>88%</td>
</tr>
<tr>
<td>Interstitial Changes (CXR)</td>
<td>8</td>
<td>47%</td>
</tr>
<tr>
<td>WBC ( \leq 4,000 )</td>
<td>8</td>
<td>47%</td>
</tr>
<tr>
<td>Platelets ( \leq 100,000 )</td>
<td>7</td>
<td>41%</td>
</tr>
<tr>
<td>SGPT ( \geq 40 \text{ IU} )</td>
<td>7</td>
<td>41%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>7</td>
<td>41%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>2</td>
<td>12%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2</td>
<td>12%</td>
</tr>
</tbody>
</table>

Data from Dummer, JID, 1985
CMV Pneumonitis

Vogel et al. Br J Radiol 2006 (epub)
CMV Pneumonitis
Cytomegalovirus Pneumonitis: Pathology
CMV Colitis
Management of CMV Infection

- Most patients receive preventive regimens, either post-transplant prophylaxis for 3 or more months or viral monitoring with preemptive therapy

- Valganciclovir is the preferred prophylaxis in the USA; some oral ganciclovir is also used. High dose valacyclovir is also used but more outside than inside the USA.

- Advantage of prophylaxis is simplicity. Some data supports better long term outcomes with prophylaxis.

- Costs of pre-emptive therapy are potentially lower and late CMV disease is less likely with pre-emptive therapy.

- Treatment of CMV disease is usually with IV ganciclovir or oral valganciclovir.
Epstein-Barr Virus (EBV) and Transplantation

- Epstein-Barr virus can cause lympho-proliferative disease after transplantation

- Some cases are polyclonal proliferations that respond to reduction of immunosuppression; others are true lymphomas

- Risk varies by transplant group - lowest in renal transplants (~0.3%) and highest in lung transplants and pediatric transplants (~4%)

- As with CMV primary infection and level of immunosuppression are the main risks
Lymphoproliferative Disease in the Abdomen related to EBV

Australas Radiol 2006;50:412
Human Herpes Virus – 8 and Kaposi’s Sarcoma (KS)

- Most recently discovered Herpesvirus
- Endemic in Central Africa (50%); also somewhat in Near East and around Mediterranean (10%); rare in USA
- Strongly associated with KS in AIDS and transplantation
- May respond to reduction of immunosuppression
Fungal Infection after Transplantation

- Mucocutaneous Candida (Thrush and esophageal candidiasis) once common but are controlled by topical antifungals such as nystatin (“swish and swallow”)

- Invasive Candida incidence varies with organ transplanted: bone marrow = liver>>lung=pancreas>heart=renal

- Cryptococcal infection occurs in 0.5-2.0 % of organ recipients usually at least 6 months out and often quite late; rare in bone marrow recipient

- Aspergillus: bone marrow>lung>liver>>heart=renal. Risk factors high dose steroids, GVHD, renal dysfunction, prolonged neutropenia

- Endemic fungal infections occur sporadically
Esophageal Candidiasis
Candidiasis in Transplantation

"I'm afraid it's a yeast infection."
Cryptococcal Infection after Transplantation

- Commonly presents either with pulmonary or central nervous system disease

- Pulmonary: usually presents with lung nodule(s) on CXR with mild pulmonary or no symptoms

- CNS disease presents as meningitis with gradual evolution of headache and neurological findings that are often subtle

- Occasionally associated skin lesions

- Diagnosis with invasive procedures (bronchoscopy, lumbar puncture and cryptococcal antigen)

- Disease can usually be controlled but some patients stay on antifungals for prolonged durations, even lifelong
Pulmonary Cryptococcosis