Transplant Related Infections

Lora Thomas MD MPH
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Risk-Benefit Ratio

- Transplantation involves a trade-off between risks and benefits
- The benefit is improved organ function and in many cases prolonged survival
- The most important risks are the toxicity of the medications and increased risk of infections
Objectives

- Review precepts of transplant infections
- Discuss sources of transplant infection:
  - Hospital acquisition
  - Endogenous reactivation
  - Donor transmission
  - Infection from environment
- Some key infections
- Managing transplant infections
## Graft and Patient Survival after Various Types of Transplantation*

<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>94</td>
<td>88</td>
</tr>
<tr>
<td>Renal-Cad</td>
<td>88</td>
<td>79</td>
</tr>
<tr>
<td>Pancreas</td>
<td>95</td>
<td>90</td>
</tr>
<tr>
<td>Heart</td>
<td>95</td>
<td>90</td>
</tr>
<tr>
<td>Liver</td>
<td>76</td>
<td>58</td>
</tr>
<tr>
<td>Heart-Lung</td>
<td>60</td>
<td>42</td>
</tr>
</tbody>
</table>

* Data from UNOS 2002 Annual Report
Change in Infectious Mortality after Cardiac Transplantation: 1980-1990

Group A 1980-85 (179 pts); Group B 1985-87 (180 pts); Group C 1987-90 (180 Pts.)
Infection Related Mortality 1990-2000

CTRD: 1990 - 1999, n=7,290

% of Patients Who Died from Specific Cause Within 3 Years

- Infection
- Graft vasculopathy
- Rejection
- Early Graft Failure
- Malignancy

Date of Transplant

Factors Contributing to Transplant Infections

- Underlying disease (E.g. Diabetes, Hep C)
- Complexity of surgery: lung & liver > heart & pancreas > kidney
- Intensity of Immunosuppression
- Immunity Prior to Transplant to specific pathogens
- Exposures after transplantation
Time Scale of Infection after Transplantation

Types of Infections vary depending on time post-transplant:

- **0-30 days:** mostly "surgical" infections. Common bacteria; also Candida, HSV

- **1-6 months:** opportunistic pathogens, cytomegalovirus (CMV), pneumocystis, fungi, Nocardia, Aspergillus

- **6 months onward:** common community infections, occasional opportunists
INCIDENCE AND TIMING OF SEVERE INFECTIONS
UNIVERSITY OF PITTSBURGH

Episodes of Infection Per Patient Per Year

- Bacterial
- Fungal
- Viral
- Protozoal

Months after Transplantation

- 1
- 2
- 3
- 4-6
- 7-12
- 12-24
- >24
## Infections in Different Transplant Groups

<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>

Infectious Episodes Related to Total Time Spent in the Operating Room

![Bar chart](chart.png)

- Infection episodes per patient
- Total operative time in hours
- n=29 for 5-10 hours
- n=42 for 10-15 hours
- n=15 for 15-20 hours
- n=5 for 20-25 hours
- n=10 for >25 hours
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
Types of Immunosuppressive Drugs

- **Calcineurin inhibitors**: cyclosporine and tacrolimus: focused effect on T cells - decrease cytokine release but nephrotoxic
- **Cytotoxic drugs**: azathioprine and mycophenylate - interfere with cell replication
- **Sirolimus/Everolimus**: affects T cell activation, not nephrotoxic
- **Steroids**: broadly anti-inflammatory and anti-lymphocytic
- **Antibodies against immune cells**: polyclonal (thymoglobulin) and monoclonal (alemtuzumab)
Comparative Infectious Risk of Immunosuppressive Agents

- Cyclosporine and tacrolimus have similar infectious risk.

- Mycophenylate is more potent than azathioprine, but may lead to more viral infections (CMV; BK virus).

- mTOR inhibitors (sirolimus) may have lower risk for some viral infections (CMV, EBV).

- Monoclonal and polyclonal antibodies against T cells impart enhanced risk for infection (E.g. ATG).

- Alemtuzumab creates a long acting immunosuppressive state. Infectious risk is higher when used to treat rejection rather than as induction to prevent rejection.

- High dose steroids increase risk for many types of infections—especially fungi and bacteria.

Halloran PF. NEJM 2004;351:2715; Dummer JS, PPID,
Some Infections Reactivate after Transplantation

- **Bacterial:** Tuberculosis
- **Viral infections:** Herpesviruses, polyomaviruses, hepatitis B virus
- **Parasites:** Toxoplasma gondii, Trypanosoma cruzi
- **Fungi:** Not well defined - Histoplasma, Cryptococcus, Coccidioides, and Pneumocystis thought to reactivate
Herpesvirus Infections after Transplantation

- **Herpes simplex** usually controlled by antiviral prophylaxis but up to 25% would have lesions without it.
- **Herpes zoster** occurs in about 20-30% of long-term recipients. Chicken pox is rare but may be fatal.
- **Epstein-Barr virus** is associated with lymphoma after transplantation. Risk varies between 0.3-4%. Risk is 10 times higher with primary infection.
- **Human herpes virus-8** is associated with Kaposi’s sarcoma after transplantation (mostly outside USA).
- **Cytomegalovirus** was the single most important pathogen in transplant recipients.
Cytomegalovirus (CMV) and Transplantation

- CMV was the most important infection after transplantation - now largely controlled by antiviral prophylaxis

- Usually reactivates 30-90 days after transplantation, but delayed in patients receiving antiviral prophylaxis

- Manifestations: Fever is most common, but invasive infection in bowel, liver, lung or retina may occur

- Risk factors for CMV disease are primary infection (usually acquired from donor), the level of immunosuppression and organ type

- Diagnosis used to be made by viral culture, now most often by rapid viral load assays E.g. quantitative PCR
Onset of Symptomatic CMV Disease
After Liver Transplantation

Number of Patients

Months After Transplantation

Disseminated CMV
Local CMV
Viral Syndrome
### Infection and Morbidity due to CMV in Different Transplant Groups*

<table>
<thead>
<tr>
<th>Type of Transplant</th>
<th>No. Patients</th>
<th>Infected Pts. (% Total)</th>
<th>CMV Disease (% Inf.)</th>
<th>Pneumonia (% Inf.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>131</td>
<td>79 (60%)</td>
<td>13%</td>
<td>4%</td>
</tr>
<tr>
<td>Heart</td>
<td>48</td>
<td>44 (92%)</td>
<td>27%</td>
<td>9%</td>
</tr>
<tr>
<td>Liver</td>
<td>93</td>
<td>55 (59%)</td>
<td>49%</td>
<td>5%</td>
</tr>
<tr>
<td>Lung</td>
<td>31</td>
<td>22 (71%)</td>
<td>55%</td>
<td>45%</td>
</tr>
</tbody>
</table>

Data collected in Pittsburgh before the introduction of routine antiviral prophylaxis

*Data from different transplant groups showing infection and morbidity due to CMV.*
CMV Pneumonitis

Vogel et al. Br J Radiol 2006 (epub)
CMV Pneumonitis

Horger et al. AJR Am J Roentgenol 2006;187:W636
Cytomegalovirus Pneumonia: Pathology
CMV Retinitis - Early
CMV Colitis

Fig. 1. The sigmoid colon showing severe submucosal haemorrhage and oedema.

Gregoor et al. Nephrol Dial Transplant
1997;12:2766
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.

- Advantage of prophylaxis is simplicity. 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 and bowel transplants and pediatric transplants (~10%)

- As with CMV primary infection and level of immunosuppression are the main risk factors
Transplant Lymphoma - Case

A 41 year old woman received a heart-lung transplant for cystic fibrosis in 1993 in North Carolina. She was EBV seronegative at the time of transplantation. She converted to EBV after transplantation possible from the donor. She maintained excellent lung function post-transplant. 13 years later she presented with a month of headache, low-grade fevers and malaise. She had left sided ptosis. An MRI scan of the head showed numerous enhancing lesions in the brain.
Initial MRI Scan of the Brain
Lymphoproliferative Disease in the Abdomen related to EBV
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
Polyomaviruses and Transplantation

- Human polyomaviruses are two related small DNA viruses (JC virus & BK virus). Serology shows most humans are infected with these viruses in childhood.
- Polyomaviruses (esp. BK but also JC) are found by culture in the urine of 10-45% of renal and bone marrow transplant patients and occasionally in normal hosts.
- JC virus causes a rare brain disease called progressive multifocal leukoencephalopathy (PML) in immunosuppressed patients.
- In recent years BK virus has been shown to cause severe nephropathy in 2-8% of renal recipients.
PVN - Staining for Polyoma virus Antigens
Polyoma virus Infection of the Transplanted Kidney: “Decoy” Cells in the Urine

Nickleit V, NEJM, 2000
Risk Factors for Polyoma virus Nephropathy (PVN) after Renal Transplantation

- The strongest risk factor is detection of virus - the disease is not seen in the absence of virus.
- Demographic risk factors are older age, male gender and caucasian ethnicity.
- Polyoma virus nephropathy is associated with the level of immunosuppression but no single drug has been consistently implicated.

Lu, ACT, 2002; Rocha PN, ACT 2003
Management of Polyoma virus Infection

- Lowering of immunosuppression improves the infection in at least half of the case but sometimes this leads to acute rejection.

- Antiviral agents that have been associated with anecdotal success include IVIG and cidofovir. None have been approved by the US Food and Drug Administration (FDA) for the treatment of BK-induced nephropathy.

- Prospective monitoring with lowering of immunosuppression in patients with high viral loads has been reported to be beneficial.

Fungal Infections after Transplantation

- **Pneumocystis:** Uncultivable agent of unknown source, recently shown to be a fungus, major pathogen in AIDS (>50%) and Transplant (3-8%) but controlled with sulfa prophylaxis.

- **Endemic soil fungus – Cryptococcus, Histoplasma etc:** Sporadic infections occur in about 1-2% of patients late after transplantation.

- **Candida, Aspergillus:** Early infections mostly seen in sicker stem cell, lung and liver transplant pts.
Pneumocystis Infection and Transplantation

- Pneumocystis pneumonia once occurred in 5-10% of transplant patients, now controlled with prophylaxis

- Typically presents with fever, hypoxemia and diffuse pneumonia 2-6 months after transplantation

- Diagnosis usually required bronchoscopy with lavage of lung alveoli (BAL GMS not as sensitive as with HIV patients)

- Treatment with sulfa-trimethoprim or pentamidine was usually successful in clearing the organism but some patients died during period of hypoxemia

- Two to three sulfa-trimethoprim tablets (DS) a week prevent it. Dapsone also appears effective
Radiographic Picture of Pneumocystis Pneumonia
Cysts of Pneumocystis in a Lung biopsy
Transplant Histoplasmosis

- Soil fungus seen mostly in south central USA. Occurs in about 0.5-1% in endemic areas.

- Pts have multisystem disease with fever, pneumonia, lymph node enlargement, low blood counts and liver and spleen enlargement.

- Diagnosis by culture (slow), urine antigen (few days) and in sickest pts by blood smear.
H. Capsulatum in a Blood smear
Cryptococcal Infection after Transplantation

- Commonly presents either with lung or central nervous system disease
- Pulmonary: usually lung nodule(s) on CXR with mild pulmonary symptoms
- CNS disease: meningitis with gradual evolution of headache and subtle neurological findings
- Occasionally associated skin lesions
- Diagnosis with invasive procedures (bronchoscopy, lumbar puncture) with culture and cryptococcal antigen
- Prognosis: patients do well unless diagnosis is delayed until there is severe neurological disease
Pulmonary Cryptococcosis
Strongly Positive India Ink Smear
Skin lesions
Due to Cryptococcus
Aspergillus infection after Transplantation

- Infection mostly is early and primarily in stem cell > lung > liver recipients
- Risk factors are low neutrophils, high doses of steroids and severe renal and liver dysfunction
- Infection starts in the lung and disseminates to other organs
- Infection can be highly lethal but prognosis is improving because of better drugs (ie voriconazole)
- Improved diagnosis with serum galactomannan
Pulmonary Nodule due to *A. fumigatus* in a Heart transplant Recipient
Pulmonary Infiltrates Caused by *Aspergillus* in a Neutropenic Host
Hyphae of Aspergillus Invading Tissue
Vascular Invasion by *Aspergillus*
Partial List of Organisms Transmitted by Transplantation

- **Viruses:** CMV and other herpesviruses, HIV, HTLV-1, hepatitis B, C & D, WNV, Rabies, Arenaviruses
- **Fungi:** Histoplasma, Coccidioides, Cryptococcus
- **Protozoa:** Toxoplasma, malaria, T. cruzii
- **Bacteria:** TB, Nosocomial pneumonia agents (lung), urinary bacteria (kidney), bacteremic donor
- **Prions:** Creutzfeldt-Jakob disease (cornea)

Transplant Infections: Some Important Exogenous Sources

- **People**: Most viruses esp. respiratory viruses, tuberculosis, some primary bacterial pathogens such as *Staphylococcus aureus* and *Streptococcus pyogenes*
- **Food and water**: *Salmonella*, *Listeria*, *Giardia*, *Cryptosporidium*
- **Animals**: Cat scratch disease, toxoplasmosis, *Pasteurella multocida*
- **Soil**: *Cryptococcus*, *Histoplasmosis*, *Coccidioidomycosis*, *Nocardia*
- **Vectors**: West Nile virus (mosquitoes), Ehrlichiosis and RMSF (ticks)
Management of Infection after Transplantation

- Attention to early diagnosis - call center for fever > 38.0
- Vaccines: transplant patients respond, but not as well as normal hosts; live vaccines are usually avoided
- Prophylaxis: works well for herpesviruses, pneumocystis, toxoplasmosis, some fungal diseases
- Monitoring: Used for most important infections (E.g. CMV quantitative PCR)
- Donor screening: Use of nucleic acid testing should lower risk of transmission at least for HIV, hepatitis viruses
- Avoidance: Not much science but patient urged to avoid high risk situations
Prevention of Exposure to Infection

- Hospital exposures: standard infection control. Bone marrow units may HEPA filter air and restrict visitors with upper respiratory infections.
- Enteric pathogens: avoid raw eggs, unpasteurized milk and juices, certain soft cheeses, stream or lake water.
- Respiratory viruses; avoid persons with colds, public places during Flu outbreaks, vaccinate family members.
- Zoonoses: avoid cat litter, bird cages, avoid jobs with frequent animal contact.
- Airborne molds: avoid barns, silos, chicken coops etc.
- Exotic infections: Before travel outside developed countries, confer with travel clinic & ID expert.
Reducing Transplant Infections

- Targeted prophylaxis with antibiotics
- Vaccines
- Modest behavioral changes in patients life to avoid infection
- Vigilance for infection: Patients should contact center when they have fever or other concerning symptoms
Role of Transplant Infectious Diseases Physician

- Be a resource for patients, physicians and medical center
- Clinical consultation in hospital and clinic (both pre and post transplant)
- Curbsides: email, pager, hallway etc.
- Help in developing infectious disease protocols
- Train residents and fellows in transplant infectious diseases
- Research and scholarship