Infections and the immunosuppressed transplant recipient
Infections in the allograft recipient

• Direct effect
• Indirect effects
  – Production of global suppression of host defences to leads to risk of super-infections (such as *Pneumocystis, Candida, Aspergillus* etc)
  – Modulation of endothelium and leucocytes leads to changes in MHC and other antigens, affecting allograft injury
  – Some infections may lead to malignancy
Organ transplants

• Donors
  – Living
    • Directed
    • Altruistic
    • Domino
  – Deceased
    • Neurological death
    • Circulatory death

• Organs
  – Kidney
  – Liver
  – Pancreas
  – Heart
  – Lung
  – Bowel
  – Face
  – Hand
  – Limb
  – Other: uterus, ovary
There are fewer potential donors

Source: Office for National Statistics

15% fall in deaths <75 yrs
Donors are older and heavier

Age of deceased donors

BMI of deceased donors
Outcomes after transplant

Long-term graft survival after first kidney only transplant from donors after brain death, 1 January 1996 – 31 December 2008

Long-term patient survival after first elective adult liver only transplant from donors after brain death, 1 January 1996 – 31 December 2008

Source: Transplant activity in the UK, 2009-2010, NHS Blood and Transplant
Classification of Infections in transplant patients (after Rubin)

• Infections related to a technical complication
• Infections related to nosocomial hazard
• Infections related to particular exposure within the community
• Viral infections of particular importance to the transplant community
Classification of Infections in transplant patients (after Rubin)

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Classification of Infections in transplant patients (after Rubin)

- Infections related to a technical complication
- Infections related to nosocomial hazard
  - *Aspergillus, Legionella, VRE, MRSA*
- Infections related to particular exposure within the community
- Viral infections of particular importance to the transplant community
Classification of Infections in transplant patients (after Rubin)

- Infections related to a technical complication
- Infections related to nosocomial hazard
- Infections related to particular exposure within the community
  - Systemic mycotic infections related to geography such as *Blastomycosis, Histoplasma*
  - Community acquired opportunistic infections from ubiquitous saprophytes as *Aspergillus, Nocardia*
  - Respiratory infections as *Myco, Flu* (incl H1N1)
- Viral infections of particular importance to the transplant community
Classification of Infections in transplant patients (after Rubin)

- Infections related to a technical complication
- Infections related to nosocomial hazard
- Infections related to particular exposure within the community
- Viral infections of particular importance to the transplant community
  - Herpes, Hepatitis viruses, Papillomavirus and HIV
With rejection you lose the graft
With infection you lose the patient
Time Table of Infections

• First month
  – Infections present prior to transplant, not eradicated or exacerbated by surgery
  – Donor derived infection
  – ‘Usual’ infections associated with major surgery
Time Table of Infections

• Months 1-6
  – Legacy of month 1 infections
  – Direct effect of immunomodulating virus
    • CMV
    • EBV
    • Hepatitis B, C
    • HIV
  – Consequence of immunosuppression and infection
    • Opportunistic infection with Aspergillus, Pneumocystis, Nocardia
Time Table of Infections

- After months 6
  - 80% have no major issues and infections similar to non-immunosuppressed patients
  - 5-15% have chronic viral infections with HBV, EBV, HHV-8, papilloma etc
  - 5-10% are at increased risk because of organ dysfunction, need for greater immunosuppression
Immunosuppression

• Varies between organ and between centres
• Induction agents
  – Anti-lymphocyte, Campath
• Maintenance agents
  – Corticosteroids
  – CNI (cyclosporin, tacrolimus)
  – Antimetabolites (azathioprine, mycophenolate)
  – mTORi (sirolimus, everolimus)
  – Anti-CTLA4 Ig (belatacept)
Induction Therapy in US
(OPTN/SRTR 2008)
Immunosuppression for maintenance at 1 year

![Graph showing immunosuppression data for 1997 and 2003]

- Tac
- Tac+MMF
- Tac+Ster
- CyA+ster
- CyA+Aza/MMF
Rituximab

- Anti CD20
- Causes lysis of B lymphocytes
- Licensed for some lymphomas
- Main issue: cytokine release syndrome
- Effective in
  - AIH
  - Severe Acute Rejection
  - Induction therapy (van der Hoogan 2010)
Antibodies to CTLA-4

- **Abatacept**
  - Fusion protein that conserves natural structure
  - Licensed for use in RhA

- **Belatacept**
  - Approved for renal transplants (with other IMS and EBV status)

From Bhat et al, Kidney International. 1=Rituximab, 4=CTLA4
Sotrastaurin (AEB071)

- Pan PKC inhibitor and blocks early T-cell activation
- Animal data shows prevents allograft rejection
- Effective in some cases of Psoriasis
- Early renal studies disappointing:
  - Combination with Tacrolimus may be more effective than with MMF (Budde 2010)
- Liver studies on-going

From Drugs of the Future (2009)
Antimicrobial prophylaxis

• Intense
  – Antibacterial
  – Antifungal
    • Usually topical antifungal treatment

• First three months
  – Anti-PCP (such as co-trimoxazole)
  – Anti-CMV
Prophylaxis against TB

• Most guidelines recommend prophylaxis in those at risk
  – Endemic countries
  – Born in high risk areas
  – Past history
  *No good data to support efficacy (Currie 2010)*

• Recent survey showed great variation in practice

• Most common is Isoniazid for 6 months
CMV

• D+/R- greatest risk which may cause reactivation or new infection

• Guidelines
  – Check CMV status pre-transplant with IgG
  – Monitoring and diagnosis
    • pp65 or quantitative CMV PCR
  – Immunohistopathology
Clinical pattern of CMV

• Asymptomatic
• Symptomatic
  – Viremia, fever, malaise
• Invasive disease
  – Hepatitis, colitis, pneumonitis, retinitis,
CMV treatment

• Prophylaxis
  – Oral valganciclovir usually for 3 months

• Active disease
  – Valganciclovir
  – Ganciclovir
  – Immunoglobulin
  – Foscarnet

Treatment is usually IV ganciclovir followed by oral valganciclovir
CMV: prophylaxis or pre-emptive treatment?

<table>
<thead>
<tr>
<th>Effect</th>
<th>Prophylaxis</th>
<th>Pre-emptive</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV disease</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Late disease</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Better graft survival</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Lymphoma/KS</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Difficult logistics</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Drug Costs</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Monitoring costs</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Resistance</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>
CMV and Rejection

- During CMV infection, IMS normally reduced
- CMV may be causally or indirectly associated with allograft rejection
- Sirolimus may have an anti-CMV effect
EBV and PTLD

- Risk factors for PTLD
  - Degree and type of immunosuppression
  - HLA matching
  - Absence of protective T cells
  *Greatest risk in small bowel recipients*
  *Impact of belatacept*

- EBV DNA monitoring
  - Rise in EBV DNA precedes PTLD on those 80%
    - EBV-driven PTLD
  - Used in high risk populations
Treatment options

- Reducing tumour burden
  - Surgery
  - Radiotherapy
  - Chemotherapy (such as R-CHOP)

- Changing immune response
  - Reducing IMS
  - Cell therapy with EBV-specific CTL
Use of EBV-CTL

• Tumour usually originates from host B cells, so CTLs should be
  – Autologous
    • First choice
    • More effective
    • Logistic issues to prepare adequate numbers
  – Allogeneic HLA-matched
    • Availability
    • Sub-optimal tumour recognition
    • May be affected by patient’s alloreactive T cells

• Clinical studies encouraging
HIV and Transplantation

• Increasing but small numbers of HIV infected patients are receiving grafts (mainly liver for end-stage HCV cirrhosis)
• Outcomes reasonable with good (50-80%) but sub-optimal survival
• Main issues are drug interactions between HAART and CNI and other IMS
HIV and liver transplantation

• Small series
• Average 1, 3 and 5 year survival 75%, 65% and 55% (compared with 92% 1 year survival and 75% 5 year survival in non-HIV)
HEV and organ transplantation

- Used to be thought a self-limiting hepatitis infection
- Several cases described of Chronic HEV with no clear risk factor
- Diagnosis by PCR
- Presents as graft non-specific hepatitis
HHV and organ transplantation

• HHV-6 A and B, HHV-7
• 1% will develop clinical illness
• Fever, malaise, hepatitis, encephalitis
• Associated with increased risk of
  – CMV disease
  – Rejection
  – Opportunistic infection
• Said to be common (1%)
• Rarely looked for
• Treatment with ganciclovir, foscarinet, cidofovir
Infections, cancer and transplantation (Engels 2011)

- SIR of possibly-infection related cancer
  - Non Hodgkin lymphoma 7.5
  - Hodgkins 3.6
  - Liver 12
  - Stomach 1.7
  - Kaposi 61
  - Oropharynx 2
  - Anus 5.8
  - Vulva 7.6
  - Cervix 1.0
Infections, cancer and transplantation (Engels 2011)

<table>
<thead>
<tr>
<th>Possibly-infection related cancer</th>
<th>Non Hodgkin</th>
<th>Hodgkins</th>
<th>Liver</th>
<th>Stomach</th>
<th>Kaposi</th>
<th>Oropharynx</th>
<th>Anus</th>
<th>Vulva</th>
<th>Cervix</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIR</td>
<td>7.5</td>
<td>3.6</td>
<td>12</td>
<td>1.7</td>
<td>61</td>
<td>2</td>
<td>5.8</td>
<td>7.6</td>
<td>1.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-infection related cancer</th>
<th>Lung</th>
<th>Kidney</th>
<th>Colo-rectum</th>
<th>Breast</th>
<th>Melanoma</th>
<th>Thyroid</th>
<th>Skin (NMSC)</th>
<th>Lip</th>
<th>Uterus</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIR</td>
<td>2.0</td>
<td>4.7</td>
<td>1.2</td>
<td>0.9</td>
<td>2.4</td>
<td>3</td>
<td>13.9</td>
<td>16.8</td>
<td>0.9</td>
</tr>
</tbody>
</table>
Donor Derived Disease
Donor Transmitted Risks

• Cancer
  – Risks of donor transmitted cancer
    • DCD donor
    • DBD donor
    • Living donor
  – Risks of donor derived cancer
  – De novo cancer

• Infection
Screening of deceased donors

- History
  - From family, family doctor, records
  - Including life-style, travel, sexual, drug use
- Review of investigations done
- Serology
  - HBV, HCV, HIV, HTLV, Syphilis, CMV

*Note:*

*limited time from consent to implantation*

*UK law prohibits testing until consent given*

*tests for infections such as West Nile, Malaria are not routinely done in UK*
Risks and Benefits
Donor Derived Infections

• Solid Organ Transplantation is associated with risk

• Mortality on the waiting list
  – Kidney 6%/year
  – Liver 17%/year
  – Heart/lung 18%/year

• Waiting lists do not reflect the need for transplantation
Generalisations

• Potential DDD in <1% donors
• Where DDD does occur, there is significant morbidity and mortality
• Significant under-reporting
• Role of donor screening uncertain
  – Impact of NAT
• Serology is unreliable for detecting DDD for HCV
### Potential Donor Derived infections
disease transmissions (OPTN 2005-9)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Reports</th>
<th>Confirmed</th>
<th>% Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virus</td>
<td>86</td>
<td>31</td>
<td>8</td>
</tr>
<tr>
<td>Bacteria</td>
<td>38</td>
<td>26</td>
<td>7</td>
</tr>
<tr>
<td>Fungus</td>
<td>30</td>
<td>26</td>
<td>8</td>
</tr>
<tr>
<td>Myco</td>
<td>26</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Parasitic</td>
<td>21</td>
<td>13</td>
<td>4</td>
</tr>
</tbody>
</table>
Infectious agents in DDD

- **Virus**
  - HCV 25
  - HIV 15
  - West Nile 14
  - HBV 13
  - HTLV 3

- **Fungus**
  - Coccidio 6
  - Histoplasma 6
  - Crypto 5
  - Candida 5
  - Zygomycetes 5
  - Aspergillus 4
Mycobacterial and parasitic DDD

• Parasitic
  – Mainly Chagas (9): screening could reduce risk

• Mycobacteria: 26 cases reported (22 TB)
  – Many recipients do not have respiratory symptoms
  – No robust screening for donors
## HIV/HCV transmissions

Risk per 1000 high risk donors screened by serology

<table>
<thead>
<tr>
<th>Group</th>
<th>HIV</th>
<th>HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemophiliac</td>
<td>0.05</td>
<td>0.46</td>
</tr>
<tr>
<td>IVDU</td>
<td>12.9</td>
<td>350</td>
</tr>
</tbody>
</table>
HIV transmission

• One instance of HIV transmission to organ recipients because of lab error in Taiwan (Parry 2011)

• Other cases rarely described
HTLV-1

• Infects 15-20 million
• High prevalence areas
  – Japan 10%, Caribbean 3-6%, Africa 1-5%
• Low prevalence areas
  – Healthy blood donors in Europe and US 0.0006% and 0.046%
HTLV associated disease

HTLV-2
• Unknown but neurological disease, lymphocytic leukemia and arthritis are reported

HTLV-1
age adjusted risk of death 1.4
• Adult T-cell leukemia
  – Life time risk of infected patients 2-5%
• HTLV-associated myelopathy
  – Life time risk of infected patients 1-2%
Screening

- ELISA
  - Sensitive but lack specificity in low risk groups
- PCR
HTLV transmitted disease

• 4 donors transmitted HTLV to 6 recipients (Only 1 confirmed HTLV)

• Outcomes of
  – death (HR 1.06)
  – graft failure (HR 1.2)
HTLV and Transplantation

• US data
  – 162 recipients of 134 repeat reactor donors identified
    no case of HTLV related disease

• UK data
  – 2004-2011 HTLV available for 1844/5984 donors
  – 4/1844 were ‘repeat reactive’
  – 8 organ recipients (6 kidney, 1 liver, 1 pancreas) followed for up to 6 years
  – None developed any HTLV-related symptoms
HBV and transplantation

• No longer a major issue
• Pre transplant HBV patients treated with anti-virals until DNA undetectable
• Post Liver transplant: HB Ig and antivirals
• Donor grafts with anti-HBc, liver recipient given long term antiviral
H1N1

• UK authorities advised against use of organs from deceased donors with H1N1
H1N1

- 5 organ donors with H1N1 at the time of donation, donated 9 kidneys, 3 livers and 1 heart
- 9 given oseltamivir
- None developed signs or symptoms of influenza
- None had H1N1 cultured
HCV and transplantation

• HCV
  – Associated with graft hepatitis and cirrhosis in accelerated form
  – Also diabetes, glomerulonephritis
  – Avoid pulsed high dose steroids

• HCV donors
  – Used for HCV-positives recipients
  – Genotype super-infection with G1 may be important
HCV treatment

• Peg-IFN and ribavirin
• Role of telaprevir and boceprevir uncertain in this indication
• Difficult because of poor tolerance
Conclusions

• De novo infections are common but usually responsive
• Donor derived infections are rare but may be serious
• De novo cancers are increased and may be related to infections