Transplantation simplified

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**HISTORY**

- The first successful kidney transplant was performed in 1954 between identical twins by Dr Joseph Murray in Boston.

- The first UK kidney transplant Edinburgh 1960.
1st renal transplant- Boston 1954

- Richard (r) and Ronald Herrick (d) identical twins
- No immunosuppression
- Lasted 8 years
- 1962 Azathioprine used for the first time for first successful kidney transplant from a deceased donor (21 months)
- Dr Joseph Murray, Boston 1954, Nobel prize 1990
- Elion and Hitchings Nobel prize 1988
Transplantation is a gold standard treatment for most patients with advanced renal insufficiency.
Adjusted First-Year Death Rates: By Treatment Modality

Deaths per 100 patient years at risk

Year of Incidence

Slide 2.

U.S. Renal Data System Annual Data Report 2001
Adjusted Relative Risk of Death among 23,275 Recipients of a First Cadaveric Transplant.

• Extends life
  • 10-15 yr

• Improves quality of life
  • No need for dialysis
  • Freedom with fluid and food intake
  • Restored fertility
  • Improved energy and ability to return to employment

• Improves quality of health
  • Significantly reduced risk of CVD

• Reduces overall medical costs and has significant public health benefit
Excretion of toxins
Excretion of excessive fluid

Control of BP

Production of erythropoietin
Correction of anaemia

Control of electrolytes: Ca/PO4/Mg/K/HCO3
Control of acid base balance
Bone health through regulation of vit D metabolism
Patients unsuitable for transplantation

- Active infection, malignancy or heart disease
- Limited life expectancy (UK >5yr; EU >2 yr) with significant comorbid conditions
- Inability to comply with immunosuppression or intolerance of main immunosuppressive agents
- Psychological disorders
Cost effectiveness of transplantation

- 3% NHS budget
- Savings per 10 yr £241,000

Cost /yr £

- Tx
- Tx 1st yr
- PD
- HD
- Dialysis
Number of deceased donors and transplants in the UK, 1 April 2003 - 31 March 2013, and patients on the active transplant lists at 31 March

Source: Transplant activity in the UK, 2012-2013, NHS Blood and Transplant
April 2013

- 6079 patients active on the National Transplant waiting list
- Average waiting time 1156 days
- Average waiting time for SPK 359 days
- Number of kidney TX April 2012-2013 :2719
- 35% Kidney Tx from live donors (969)
Long-term graft survival after first adult kidney only transplant from donors after brain death, 1 January 1999 – 31 December 2011

Source: Transplant activity in the UK, 2012-2013, NHS Blood and Transplant
Long-term graft survival after first adult living donor kidney only transplant in the UK, 1 January 1999 – 31 December 2011

Source: Transplant activity in the UK, 2012-2013, NHS Blood and Transplant
### Optimal outcomes of renal transplantation

<table>
<thead>
<tr>
<th>Optimal preparation for transplantation</th>
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<tbody>
<tr>
<td>Optimal timing</td>
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<tr>
<td>Optimal donors</td>
</tr>
<tr>
<td>Good surgical technique</td>
</tr>
<tr>
<td>Good early post transplant care</td>
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<tr>
<td>Optimal immunosuppression regimes</td>
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<tr>
<td>Optimal follow up care</td>
</tr>
<tr>
<td>Minimization of cardiovascular risk factors</td>
</tr>
</tbody>
</table>
Transplantation is not easy…

- Need for surgery
- Need for immunosuppressive medication
- Need for regular and lifelong follow-up
- Fear of transplant failure
Transplantation - risks

- Risks associated with the surgery
- Rejection

- Side-effects of immunosuppression
- Infective risks-opportunistic infections
- Increased risk of malignancy
Early complications

- Delayed graft function (50% of DCD kidneys)
- Wound infection
- UTI
- Fluid overload
- Electrolyte disturbances
- Vascular anastomotic thrombosis
- Obstruction
  - Bladder outflow
  - Ureteric stenosis
Acute rejection rate within 1st post transplant year

Patients age 18 & older.
Rejection

- AR rate within 12 months ~10-15%
- Acute cellular rejection
  - Grades depending on severity
- Antibody mediated rejection
- Treatable 90%
Induction
- Steroids (MP)
- Anti CD25 Basiliximab
- ATG
- Campath/ alemtuzumab

Maintenance immunosupression
- Calcineurin inhibitors: Tacrolimus/ Ciclosporin
- Antimetabolite: MMF
- Steroids

Adjustments
- Switch to mTOR inhibitors
- Steroid withdrawal
- Monotherapy
KI 7.4 Immunosuppression use in adult kidney transplant recipients

SRTR&OPTN Annual Report 2011
KI 7.1 Initial immunosuppression regimen in adult kidney transplant recipients, 2011
Calcineurin inhibitors

- Narrow therapeutic range - need for monitoring
- Nephrotoxicity/ hypertension/ dyslipidaemia/ DM
- Tacrolimus preferred (lower AR / possible improved allograft survival)
- Better tolerated and preferred by patients
- Acceptable rates of NODAT
- Decreased doses of MMF permissible
CyA side effects
Tacrolimus

- Macrolide antibiotic
- Discovered 1984 by fermentation of Japanese soil containing bacteria Streptomyces Tsukubaensis
- FDA approved 1994
Tacrolimus: mode of action

- Binds to an immunophilin FKBP
- Complex blocks calcineurin mediated T cell receptor signal transduction and IL2 gene transcription
- Suppresses T cells and T cell dependent B cell activation
MMF/Myfortic

- Reversible inhibitor of inosine monophosphate dehydrogenase (IMDH)
- Enzyme is essential in purine biosynthesis necessary for T and B cell proliferation and growth
- Potent inhibitor of immunity
- Side effects: GI, bone marrow suppression
- Contraindicated in pregnancy
Immunosuppression

- Combination therapy (agents with different mechanism of action)
- Maximal immunosuppression in early post transplant period when immunological risks are highest
- Slow tapering of immunosuppression
- Specific patients characteristics influence the choice of immunosuppression
Immunosuppression

- Rejection
- Infection Malignancy
Cumulative Probability of Biopsy-Proven Acute Rejection (Panel A) and Allograft Survival (Panel B),
Low Tacrolimus dose based IS regime- gold standard in 2015

Late complications

- Cardiovascular disease and hypertension
- Hyperlipidaemia
- Post transplant diabetes mellitus
- Erythrocytosis
- Malignancy
- Infections
- Recurrent disease
# Infections

<table>
<thead>
<tr>
<th>1&lt;sup&gt;st&lt;/sup&gt; months</th>
<th>1-6 months</th>
<th>After 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post op bacterial infections: UTI, URTI, LRTI, Wound, Candida</td>
<td>Opportunistic: <strong>CMV</strong>, VZV, RSV, Aspergillus, Cryptococcus, Nocardia, listeria, mycobacterium, Legion Ella, <strong>PCP</strong>, Toxoplasma</td>
<td>CMV retinitis and colitis, Cryptococcus, Parvo virus B-19, polyoma virus, TB, Oncogenic viruses, Unusual sites</td>
</tr>
</tbody>
</table>
BK nephropathy

- Evolving challenge in kidney transplant recipients
- Consequence of modern potent immunosuppression
- Untreated it leads to allograft dysfunction or loss (35-67% within a year)
- Decreased immunosuppression is the principle treatment but predisposes to graft loss (8-12% risk of ACR)
BK polyoma virus infection affecting Tx
BK virus

- Polyoma virus (papoviridae family)
- Small DNA virus 30-45 nm
- First described in 1971
- 4 other human Polyoma viruses JC/KI/WU/MCV
- BK only cause of nephropathy in immunocompromised patients
BKV infection

- Tropism for genitourinary tract
- Clinical manifestations:
  - Asymptomatic haematuria
  - Haemorrhagic and non haemorrhagic cystitis
  - Urethral stenosis
  - BK nephritis (tubulo-interstitial nephritis)
Management of BKV infection

- Screening and preemptive strategy
  - Monitoring for viraemia
  - Decrease in immunosuppression after detection of very early systemic infection

- Treatment strategy
  - Decrease in immunosuppression +/- antiviral agents on biopsy verified or presumptive diagnosis of BKVN

85% clearance

Immunosuppression

Rejection
MALIGNANCY:
Comparison of the Incidence of Malignancy in Recipients of Different Types of Organ: A UK Registry Audit

MALIGNANCY: INCREASED RATES/RISK

Table 3: Standardized Incidence Ratios (95% confidence intervals) for malignancy in recipients of different organs

<table>
<thead>
<tr>
<th>Site of cancer</th>
<th>Kidney</th>
<th>Liver</th>
<th>Heart</th>
<th>Lung</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cancers (excluding nonmelanoma skin cancer)</td>
<td>2.4 (2.3, 2.5)</td>
<td>2.2 (2.0, 2.4)</td>
<td>2.5 (2.2, 2.7)</td>
<td>3.6 (3.0, 4.4)</td>
</tr>
<tr>
<td>Skin: nonmelanoma</td>
<td>16.6 (15.9, 17.3)</td>
<td>6.6 (5.8, 7.5)</td>
<td>18.5 (16.9, 20.3)</td>
<td>16.1 (13.1, 19.6)</td>
</tr>
<tr>
<td>Lip</td>
<td>65.6 (49.9, 84.6)</td>
<td>20.0 (5.4, 51.2)</td>
<td>60.0 (31.0, 104.8)</td>
<td>1</td>
</tr>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>7.4 (5.3, 10.2)</td>
<td>8.9 (3.8, 17.5)</td>
<td>11.4 (4.9, 22.5)</td>
<td>5.0 (0.1, 27.9)</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>12.5 (11.2, 13.8)</td>
<td>13.3 (10.6, 16.6)</td>
<td>19.8 (16.1, 24.1)</td>
<td>30.0 (20.6, 42.1)</td>
</tr>
<tr>
<td>Breast</td>
<td>1.0 (0.8, 1.2)</td>
<td>0.8 (0.5, 1.1)</td>
<td>0.8 (0.3, 1.7)</td>
<td>0.3 (0.0, 1.2)</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>4.2 (2.9, 5.9)</td>
<td>10.0 (5.9, 15.8)</td>
<td>5.0 (2.2, 9.8)</td>
<td>5.0 (0.6, 18.1)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>1.8 (1.6, 2.1)</td>
<td>2.3 (1.7, 3.0)</td>
<td>1.1 (0.7, 1.7)</td>
<td>1.1 (0.3, 2.9)</td>
</tr>
<tr>
<td>Anus</td>
<td>10.0 (6.6, 14.6)</td>
<td>3.3 (0.4, 12.0)</td>
<td>7.5 (1.6, 21.9)</td>
<td>20.0 (2.4, 72.2)</td>
</tr>
<tr>
<td>Liver</td>
<td>2.4 (1.5, 3.8)</td>
<td>2</td>
<td>1.2 (0.2, 4.5)</td>
<td>10.0 (2.1, 29.2)</td>
</tr>
<tr>
<td>Lung and bronchus</td>
<td>1.4 (1.2, 1.6)</td>
<td>1.6 (1.2, 2.2)</td>
<td>2.1 (1.6, 2.8)</td>
<td>5.9 (3.7, 8.8)</td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
<td>17.1 (8.9, 30.0)</td>
<td>0.0</td>
<td>10.0 (0.2, 55.7)</td>
<td>1</td>
</tr>
<tr>
<td>Kidney</td>
<td>7.9 (6.7, 9.3)</td>
<td>1.8 (0.8, 3.6)</td>
<td>4.4 (2.5, 7.0)</td>
<td>2.5 (0.3, 9.0)</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>3.3 (2.3, 4.6)</td>
<td>0.8 (0.1, 3.0)</td>
<td>3.2 (1.2, 6.9)</td>
<td>2.5 (0.1, 13.9)</td>
</tr>
</tbody>
</table>

1 SIR cannot be calculated for two cancers in lung transplant recipients where the observed number of cases is 1 and the corresponding expected number is zero.

2 All occurrences of liver cancer in liver recipients are assumed not to be de novo.

MALIGNANCY: POOR OUTCOMES WITH TREATMENT

Farrugia D et al. KI 2014;85: 1395-1403 (2)
Skin cancer

- SIR ~14  (14X more common than in general population)
- More aggressive
- Can be metastatic
PTLD

- Most common malignancy complicating solid organ transplantation *(21%)*
- The most serious and potentially fatal complication of immunosuppression
- Mostly large cell lymphoma of B cell type, but cases of T cell and NK cells have been reported
Incidence

- 1-2% SOT
- 30-50 times higher than in general population
- Recent trend towards increased frequency
- Significant variability with different types of transplants:
  Multiorgan > intestinal > lung > heart > renal > liver
Pathogenesis

- B cell proliferation induced by infection with Epstein-Barr virus in the setting of chronic immunosuppression*
- Most PTLD cells are of the host origin, but cases of PTLD localized within the graft can be of donor origin
- PTLD not directly associated with EBV present much later and are associated with worse outcomes
Risk factors

- Younger age (higher percentage EBV negative)
- History of pre transplant malignancy
- Negative EBV status of the recipient (RR 7.7-24)
- Overall level of immunosuppression
  - Certain types of induction therapy: ATG/OKT3
  - No evidence that Alemtuzumab (anti CD 52) or Basiliximab (anti CD 25) increase the risk
- Fewer HLA matches (especially on B loci, RR5)
Clinical manifestations

- Early non specific symptoms: fever, weight loss, malaise, night sweats
- Often extra nodal masses (50%)
- 20-25% CNS disease (rare in general population)
- 25% localized in the allograft with organ dysfunction

MEAN TIME 20-35 months post transplant
Monoclonal PTLD

- The anti-CD20 monoclonal antibody (RETUXIMAB) along with reduction of immunosuppression Chemotherapy (CHOP/ProMACE-CytaBOM….)
- Interferon $\alpha$ but high risk of inducing acute organ rejection
REGRESSION OF PTLD WITH IS REDUCTION

MMF 1g bd
Tac 4mg
Pred 0

MMF 500mg bd
Tac 1mg
Pred 10mg

MMF 0
Tac 1mg
Pred 7.5mg
Prognosis

- Depends on clonality and the extent of the disease
- Overall survival rate 25-35%
- With monoclonal and CNS disease mortality 80%
- T cell lymphoma have very poor prognosis
Post transplant DM

- 4-20% of Tx recipients
- 4% require Insulin
- Corticosteroids and Tacrolimus
- Risk factors for NODAT:
  - Acute rejection
  - Age>45
  - Male sex
  - Weight gain
Cumulative incidence of NODAT

Patients receiving a first-time, kidney-only transplant, 2002–2006 combined.
Causes of late graft loss

* CAN- Chronic allograft nephropathy
Causes of death with function

- Unknown: 23%
- Infection: 27%
- Malignancy: 12%
- CVD: 38%

First-time, kidney-only transplant recipients, age 18+, 2005–2009, who died with functioning graft.
Kaplan-Meier Analysis of Allograft Loss Due to Recurrence of Glomerulonephritis, Acute Rejection, Chronic Rejection, and Death with a Functioning Allograft

Recurrent diseases in renal transplants

<table>
<thead>
<tr>
<th>Disease</th>
<th>Clinical recurrence rate (%)</th>
<th>Graft loss in recurrent disease (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary FSGS</td>
<td>20-50 children 10-15 adults</td>
<td>40-50</td>
</tr>
<tr>
<td>Membranoproliferative GN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>type I</td>
<td>20-30 80-100</td>
<td>30-40 &lt;20</td>
</tr>
<tr>
<td>type II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HUS; Classical D+</td>
<td>0-13 30-50 57</td>
<td>? 55-100 100</td>
</tr>
<tr>
<td>Atypical D- Familial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgA</td>
<td>29-39</td>
<td>16-33</td>
</tr>
<tr>
<td>Membranous</td>
<td>&lt;10</td>
<td>50</td>
</tr>
</tbody>
</table>
Kaplan-Meier Analysis of Allograft Loss Due to Recurrence of Glomerulonephritis, According to the Type of Glomerulonephritis

Follow-up post transplantation

- Meticulous, life long
- Balancing immunosuppression and risk of rejection with the risks of over-immunosuppression (malignancy/infection)
- Modification and control of risk factors associated with CVD (BP/DM/Cholesterol)
Summary

- Transplantation is life saving not just health enhancing therapy
- Transplant patients have better health and lower rate of cardiovascular disease
- Inconvenience of dialysis is removed
- Psychological wellbeing often improved
- Ability to lead near normal and productive life restored
- Significant cost savings for the NHS