Transplantation: Solid Organs (Kidney)

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Overview

1. Introduction

2. Histocompatibility Tests and HLA-Antigens

3. Immunosuppression

4. Immunological Problems in Clinical Practice

5. Novel Directions
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Solid Organ Transplantation in Switzerland
Kidney Waiting List and Transplants: 1999 - 2008

Transplantations

<table>
<thead>
<tr>
<th>Year</th>
<th>Kidney WL</th>
<th>Kidney TX</th>
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<tbody>
<tr>
<td>1999</td>
<td>254</td>
<td>1</td>
</tr>
<tr>
<td>2000</td>
<td>256</td>
<td>2</td>
</tr>
<tr>
<td>2001</td>
<td>228</td>
<td>2</td>
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<tr>
<td>2002</td>
<td>204</td>
<td>1</td>
</tr>
<tr>
<td>2003</td>
<td>283</td>
<td>1</td>
</tr>
<tr>
<td>2004</td>
<td>259</td>
<td>1</td>
</tr>
<tr>
<td>2005</td>
<td>260</td>
<td>1</td>
</tr>
<tr>
<td>2006</td>
<td>276</td>
<td>1</td>
</tr>
<tr>
<td>2007</td>
<td>261</td>
<td>1</td>
</tr>
<tr>
<td>2008</td>
<td>286</td>
<td>1</td>
</tr>
</tbody>
</table>

Total Kidney WL: 664
Total Kidney TX: 286

1999-2008 Kidney Waiting List and Transplantations.
Organ Donation in Europe per Mio. Inhabitants 2008

[Map showing organ donation rates per million inhabitants across Europe]
Evolution of Organ Donation in Switzerland 1999-2008
Living Donors vs Deceased Donors
1092 Living Kidney Donors in SOL-DHR
April 1993 – August 2008

Anzahl

<table>
<thead>
<tr>
<th>Category</th>
<th>Frauen</th>
<th>Männer</th>
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<tbody>
<tr>
<td>Partner</td>
<td>262</td>
<td>93</td>
</tr>
<tr>
<td>Parents</td>
<td>208</td>
<td>107</td>
</tr>
<tr>
<td>Brother or Sister</td>
<td>167</td>
<td>122</td>
</tr>
<tr>
<td>Non-related donors</td>
<td>47</td>
<td>31</td>
</tr>
<tr>
<td>Living related donors</td>
<td>39</td>
<td>16</td>
</tr>
</tbody>
</table>
Reduction of GFR (CrCl) due to nephrectomy (SOL-DHR)

Percentage loss of CrCl

♂ ≈ 27%↓
♀ ≈ 25%↓

SOL-DHR July 2004
Situation of organ donation in Switzerland

• Low organ donation rate compared to other countries in Europe

• Severe organ shortage despite major efforts!

• Typical donor: 52 y. old patient with death due to a cerebral hemorrhage!

What about the laws?
Swiss Law on Transplantation

Bundesgesetz über die Transplantation von Organen, Geweben und Zellen
(Transplantationsgesetz)

Verordnung über die Transplantation von menschlichen Organen, Geweben und Zellen
(Transplantationsverordnung)

Verordnung über die Zuteilung von Organen zur Transplantation
(Organzuteilungsverordnung)
Swiss Organ Allocation System (SOAS)

Swiss Organ Allocation System (SOAS)

Allocation

Tx-centers

Swisstransplant

- SOAS: Internet-based program for organ allocation
- Management = Swisstransplant: National allocation organisation mandated by BAG
**Bundesgesetz über die Transplantation**

Art. 17 **Nichtdiskriminierung**

1 Bei der Zuteilung eines Organs darf niemand diskriminiert werden.

2 Personen mit Wohnsitz in der Schweiz sind bei der Zuteilung gleich zu behandeln.

Art. 18 **Massgebende Kriterien**

1 Für die Zuteilung sind insbesondere folgende Kriterien zu berücksichtigen:
   a. die medizinische Dringlichkeit einer Transplantation;
   b. der medizinische Nutzen einer Transplantation;
   c. die Wartezeit.
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Anatomy of Kidney Transplantation
Histocompatibility tests prior to Transplantation

- ABO blood type
- Determination of PRA (Panel Reactive Antibodies)
- HLA tissue typing (HLA-A, -B, -DR)
- T- and B-Lymphocyte Cross-Match (Recipient_{Serum} - Donor_{Lymphocytes})
I - Determination of Blood Group

- Donor and recipient *should* be ABO compatible
- Endothelial cells express A or B antigens
- Pre-existing antibodies to the lacking antigens
II - PRA (Panel-Reactive Antibodies)

- Preformed antibodies in the serum of a potential recipient against HLA molecules of lymphocytes from a panel of 56 normal subjects: e.g. antibodies against 28/56 = PRA of 50%
- The higher the PRA, the more “sensitized” the recipient!
III - HLA Tissue Typing

- Donor and recipient HLA alleles
- HLA A, B & DR (DQ) are most important
- Two alleles for each gene = total of 6 antigens
- Range of HLA compatibility: 0 antigen mismatch to 6 antigen mismatch
- Important for organ allocation
Map of the HLA Region on Chromosome 6

MHC (HLA) CLASS I: HLA-A, HLA-B, HLA-C
MHC (HLA) CLASS II: HLA-DP, HLA-DQ, HLA-DR
Donor-specific HLA-Antibodies (DSA)

• Quantification of antibodies in the serum of a transplant recipient against specific HLA molecules (of a donor) by flow cytometry (Luminex)
High PRA (Panel-Reactive Antibodies) and HLA-Antibodies

- Pregnancy
- Blood transfusions
- Prior transplant

“high risk” for rejection
IV - Lymphocyte Cross-Match

- Donor T-/B-lymphocytes are incubated against recipient serum
- Determines if recipient has circulating antibodies against donor lymphocytes (HLA antigens)

1) Plate with donor's lymphocytes
2) Complement
3) (Potential) recipient's serum
2 types of immune reactions

- **T cells contact with antigen**
  - Activation of Reactive T cells
  - Proliferation T cells
  - Lymphocytic infiltration
  - **Cellular Immune reaction**

- **B cells contact with antigen**
  - Activation of Reactive B cells
  - Proliferation B Cells
  - Anti HLA Antibodies
  - **Humoral Immune reaction**

- **IL-2**
- **IL-4**
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### Modes of Action of important Immunosuppressants

<table>
<thead>
<tr>
<th>Category</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Calcineurin inhibitors</strong></td>
<td>Cyclosporine, Tacrolimus</td>
</tr>
<tr>
<td><strong>Purine synthesis inhibitors</strong></td>
<td>Azathioprine, Mycophenolic Acid (Cellcept®/Myfortic®)</td>
</tr>
<tr>
<td><strong>Pyrimidine synthesis inhibitor</strong></td>
<td>Leflunomide, FK778</td>
</tr>
<tr>
<td><strong>Nonspecific</strong></td>
<td>Prednisone</td>
</tr>
<tr>
<td><strong>Target of rapamycin inhibitor</strong></td>
<td>Rapamycin (Sirolimus®/Certican®)</td>
</tr>
<tr>
<td><strong>Polyclonal T-cell antibodies</strong></td>
<td>Thymoglobuline®, Atgam®</td>
</tr>
<tr>
<td><strong>Monoclonal T-cell antibodies</strong></td>
<td>IL-2 receptor antagonists: Daclizumab (Zenapax®), Basiliximab (Simulect®)</td>
</tr>
<tr>
<td></td>
<td>OKT3 (anti-CD3)</td>
</tr>
<tr>
<td><strong>Co-stimulation blockade</strong></td>
<td>Belatacept (LEA 29Y)</td>
</tr>
</tbody>
</table>
Immunosuppressive Agents: Action on T-cells

- Cyclosporine
- Tacrolimus
- IL-2 Antagonists
  - IL-2 R (High affinity)
- OKT3
- ATG
- Belatacept
- Antigen Presenting Cell
- Activated T-cell
- PROLIFERATION
- Rapamycin
- MPA/MMF
- Leflunomide/Azathioprine
Cyclosporine/Tacrolimus = Calcineurin Inhibition

CaN = Proteine phosphatase 3B
Cyclosporine/Tacrolimus: Metabolism and clearance

- Available dose
- Eliminated dose

To faeces 15%
Metabolism 45%
First-pass metabolism 10%

Available dose
Eliminated dose

Gut lumen
Gut wall
P-gp
CYP3A4
Portal vein
Liver

25-35% to blood
Myfortic® (MPA): comparison with CellCept® (MMF)

**Myfortic**
- 720 mg b.i.d. (2 x 360 mg tablets)
- Mycophenolate sodium – salt
- Active moiety: mycophenolate
- Delayed release, enteric-coated
- Release in small intestine

**Cellcept**
- 1000 mg b.i.d. (2 x 500 mg tablets)
- Mofetil ester – prodrug
- Active moiety: mycophenolate
- Immediate release

**Mechanism:** Inhibition of IMPDH-2 for de novo purine synthesis

**Side effects:** anemia, leukopenia, diarrhea, abdominal pain
Everolimus und Sirolimus (Rapamycin): comparison

- **Half life**: 28 hrs
- **Time until steady state**: 4 days
- **Loading-Dosis** nor necessary

- **Half life**: 60 hrs
- **Time until steady state**: 6 days
- **Loading-Dosis** necessary

**Trough levels**: 4-8 ng/ml
T-Cells Require Costimulation for Full Activation

TCR signal only = no activation

- No cytokine production
- No cell division
- Becomes anergic
- Undergoes apoptosis

APC = antigen-presenting cell; TCR = T-cell receptor; MHC = major histocompatibility complex
T-Cells Require Costimulation for Full Activation

CD80/86-CD28 is the most important costimulatory pathway*

Signal 1
Antigen triggers T-cell receptor

Signal 2
Costimulation between ligands

APC=antigen-presenting cell

*Other costimulatory pathways exist that also serve this role
CTLA4 Negatively Regulates T-cell Activation

- CTLA4 (CD152) expression is induced by T-cell activation
- CTLA4 is structurally similar to CD28
- CTLA4 binds CD80/86 with greater avidity than CD28
- CTLA4 negatively regulates T-cell activation
Belatacept blocks T-cell activation

- No cell division
- No cytokine production
- Anergy
- Apoptosis

**Belatacept: CTLA4Ig human fusion protein**

Selective co-stimulation blocker

- CD80 (B7-1)
- CD86 (B7-2)
- CD28
- MHC
- TCR
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## Classification of Renal Allograft Histology

### Banff’05 diagnostic categories for renal allograft biopsies

1. Normal
2. Acute or chronic active antibody-mediated rejection
3. Borderline changes
4. Acute or chronic active T-cell-mediated rejection
5. Interstitial fibrosis and tubular atrophy, no evidence of specific etiology ("chronic allograft nephropathy")
6. Other changes

American Journal of Transplantation, 2007
Acute cellular rejection
(tubulointerstitial and vascular reactions)
Acute humoral rejection

Neutrophile granulocytes in peritubular capillaries

C4d in peritubular capillaries
Causes of graft loss after kidney transplantation

- IF/TA: 40%
- Disease recurrence: 10%
- Death with function: 40%
- Other: 10%

„chronic rejection“

Constant Renal Allograft Loss after 1 Year

Pascual M, NEJM, 2002
Donor Relationship
First Kidney Transplants 1997-2007

% Graft Survival (log)

Years

HLA-Id Sibl  n= 3,084
1-Hapl Rel  n=13,302
Deceased  n=88,837

<table>
<thead>
<tr>
<th>Donor Relationship</th>
<th>10-Year Estimate</th>
<th>Half-Life (Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-Id Sibl</td>
<td>85 %</td>
<td>50.8</td>
</tr>
<tr>
<td>1-Hapl Rel</td>
<td>73 %</td>
<td>24.3</td>
</tr>
<tr>
<td>Deceased</td>
<td>64 %</td>
<td>19.0</td>
</tr>
</tbody>
</table>
Main Causes of Renal Allograft Loss

![Graph showing the main causes of renal allograft loss](image)

- Death
- IF/TA (Chronic Rejection)
- Acute Rejection

Percent of Graft Losses vs. Recipient Age
Interstitial Fibrosis / Tubular Atrophy (IFTA)

glomerulopathy, interstitial fibrosis, tubular atrophy.

Ferlicot Sophie, Hôpital Bicetre, Paris
Main Causes of Renal Allograft Loss

- Death
- IF/TA (Chronic Rejection)
- Acute Rejection

Clinical Transplants 2001
Causes of death after kidney transplantation

USRDS adult, 1st kidney-only transplants, 1995–2003

Patients who died with functioning graft (n=10,648)
Complications of Immunosuppression: Infections

CMV Pneumonia

Herpes Zoster
Nocardia pneumonia

**Symptoms:** « slightly tired, temperature 37.5°C »

Patient history:
Since 1996 recurrent spinalioms

Current Dx:
2006, metastatic squamous cell carcinoma →
Neck dissection.
Exitus letalis (Creatinin 145 µmol/l !)
Complications: All Types of Malignant Tumors
Deceased Donor Kidney Recipients

Cumulative Incidence (per 100,000)

Patients n=197,529

- Kaposi's (6%)
- Lymphomas (24%)
- Skin and lip (34%)
- Other (36%)

Years

Patients Expected

CTS Collaborative Transplant Study 2008

K-51109-0808
Relative Risk of Death among 23,275 Recipients of a First Cadaveric Kidney Transplant (Tx)

<table>
<thead>
<tr>
<th>Dx ESRD</th>
<th>Years WL</th>
<th>Years Tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes:</td>
<td>8</td>
<td>19</td>
</tr>
<tr>
<td>GN:</td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td>Other:</td>
<td>12</td>
<td>20</td>
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</tbody>
</table>

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Transplantation Across ABO Incompatibility
ABO-incompatible Transplantation
Karolinska Schema

-4 We -10 -6 -4 -2 -1

Rituximab Glycosorb TAC MMF Pred

Glycosorb

Tx d 3 + ?
ABO-Incompatible Kidney Transplantation Using Antigen-Specific Immunoabsorption and Rituximab: A 3-Year Follow-up

Helena Genberg,1,2,6 Gunilla Kumlien,3,4 Lars Wennberg,1,2 Ulla Berg,5,2 and Gunnar Tydén1,2

FIGURE 1. Cumulative event-free survival time in adult patients: time to death, graft loss or first rejection. “Time to event” was defined as time to first rejection, graft loss, or death. Using chi-square test, $P=$ non-significant.
Domino paired Exchange

Donor #1: Altruistic
Honore Rothstein
R. Montgomery, M.D.
GOR Room 4

Donor #2
Florence Jantz
Li-Ming Su, M.D.
GOR Room 18

Donor #3
Sharon Brooks
M. Tan, M.D.
GOR Room 2

Donor #4
Leslie Persell
D. Segal, M.D.
GOR Room 1

Donor #5
Sandra Loeven
J. Melanson, M.D.
GOR Room 3

Recipient #1:
Kristine Jantz
R. Montgomery, M.D.
GOR Room 4

Recipient #2:
George L. Brooks:
W. Maley, M.D.
GOR Room 5

Recipient #3:
Gary Persell
M. Tan, M.D.
GOR Room 2

Recipient #4:
Gerald Loeven
D. Segal, M.D.
GOR Room 1

Recipient #5:
Sheila Thornton
J. Melanson M.D.; J. Cameron, M.D.
GOR Room 3

Parent: Child
Married
Married
November 14, 2006

5 Way Domino Transplant
Brief Report

HLA-Mismatched Renal Transplantation without Maintenance Immunosuppression

Tatsuo Kawai, M.D., A. Benedict Cosimi, M.D., Thomas R. Spitzer, M.D., Nina Tolkoﬀ-Rubin, M.D., Manikkam Suthanthiran, M.D., Susan L. Saidman, Ph.D., Juanita Shaffer, B.S., Frederic I. Preffer, Ph.D., Ruchuang Ding, M.D., Vijay Sharma, Ph.D., Jay A. Fishman, M.D., Bimalangshu Dey, M.D., Dicken S.C. Ko, M.D., Martin Hertl, M.D., Nelson B. Goes, M.D., Waichi Wong, M.D., Winfried W. Williams, Jr., M.D., Robert B. Colvin, M.D., Megan Sykes, M.D., and David H. Sachs, M.D.