Renal Transplantation; where do we stand today?

Ioannis Griveas
Key Issues in Organ Transplantation

- Organ shortage

- Chronic rejection

- Long-term complications of permanent immunosuppression:
  - malignancies, infections, organ toxicities
# Factors influencing long-term outcome

<table>
<thead>
<tr>
<th>DONOR</th>
<th>RECIPIENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>age</td>
<td>age</td>
</tr>
<tr>
<td>source</td>
<td>preformed Ab</td>
</tr>
<tr>
<td>HLA match</td>
<td>immune reactivity</td>
</tr>
<tr>
<td></td>
<td>waiting time</td>
</tr>
<tr>
<td></td>
<td>viral status</td>
</tr>
<tr>
<td></td>
<td>specific diseases</td>
</tr>
<tr>
<td></td>
<td>calcineurin-inhibitors</td>
</tr>
<tr>
<td></td>
<td>factors progression</td>
</tr>
<tr>
<td></td>
<td>tx glomerulopathy</td>
</tr>
<tr>
<td></td>
<td>chronic rejection</td>
</tr>
</tbody>
</table>
Background History

Haemagglutination was the technique first used – and that continues to be used.

1910 – shown to have inherited characteristics
1950s represented oligosaccharides
1990 the gene encoding the enzymes responsible for synthesis of ABO antigen was cloned.
ABOi therapy

ANTIBODY REMOVAL
- Plasma exchange
- Double Filtration Plasma Exchange
- Immunoabsorption

ANTIBODY SUPPRESSION
- Splenectomy
- Anti-CD20
- Anti-CD52
- IV Ig
**TABLE 4.** Patient and graft survival among 60 ABOi kidney transplant recipients transplanted at the Johns Hopkins Hospital between 1999 and 2007

<table>
<thead>
<tr>
<th>ABOi cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years posttransplant</td>
</tr>
<tr>
<td>------------------------------------</td>
</tr>
<tr>
<td>1 yr</td>
</tr>
<tr>
<td>3 yr</td>
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<tr>
<td>5 yr</td>
</tr>
</tbody>
</table>

Reported survival was determined using Kaplan-Meier estimation.

<sup>a</sup> Death-censored graft survival; 4 graft losses occurred in the first era cohort and were secondary to non-compliance (n=1), recurrent disease (n=2), and thrombotic microangiopathy (n=1).

<sup>b</sup> All 3 patients died with a functioning graft; 3 patient deaths were secondary to West Nile virus, sudden cardiac death, and metastatic liver cancer.

ABOi, ABO incompatible.
Maastricht classification

- Category I- dead on arrival-uncont.
- Category II- Failed resuscitation-uncont.
- Category III- Awaiting cardiac arrest-controlled
- Category IV-Cardiac arrest, brain dead-controlled
- Category V- Unexpected cardiac arrest in ITU

* Target figures taken from the UK Transplant business case
WOULD I BE WILLING TO DONATE A KIDNEY?

NO!
YES to my child - parent - sibling - relative - partner or even friend

FEARS: risks of pre-op testing
potential surgical complications, all: 12.2% - 63% (13 centers)
complications, severe: 0% - 13% (18 centers)
risks of anesthesia: complications: 1 in 10,000 – 30,000
jeopardize my own long term health
physical stress (pain)
psychological stress due to high expectations 1) unsuccessful result?
  2) Do I even want to
know exactly how
(un)healthy I am?
  3) change in relationship
  4) paternity?

MOTIVES: social pressures (family, society, associates)
  it’s not fair, I’m healthy, you’re not - bad conscience
good reputation, raise your self esteem (I’m a hero!)
  improve my own quality of life (healthy partner)
Guidelines for living kidney-donors

1) Check the health of the donor including BMI
2) Consider any alternative treatment available for the recipient (Transplantation vs Dialysis)
3) Make the risks clear
4) Elucidate the motivation

Laparoscopic Living Donor Nephrectomy For Kidney Transplantation
Stephen T. Bartlett, M.D., Eugene J. Schweitzer, M.D.

less pain, shorter hospitalisation, rapid return to normal activity, improved cosmetic result
Risks associated with donation

Possible long term complications:

- Hypertension/proteinuria
- Quality of life compromised
- Long term mortality increased?
**Risk for proteinuria**

Follow-up of 63 donors for about 20 years

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Present</th>
<th>Controls=50 donor sibling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteinuria</td>
<td>0%</td>
<td>8%</td>
<td>9%</td>
</tr>
</tbody>
</table>

- Najarian JS, Chavers BM, McHugh LE, Matas AJ. 20 years or more of follow-up of living kidney donors. Lancet 1992, 340: 807

**Risk for hypertension**

Follow-up of 63 donors for about 20 years

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Present</th>
<th>Controls=50 donor sibling</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP</td>
<td>118/76</td>
<td>134*/80</td>
<td>130/80</td>
</tr>
<tr>
<td>BP medication</td>
<td>0%</td>
<td>32%</td>
<td>44%</td>
</tr>
</tbody>
</table>

- Najarian JS, Chavers BM, McHugh LE, Matas AJ. 20 years or more of follow-up of living kidney donors. Lancet 1992, 340: 807

**Results from the metanalysis**

- GFR reduction 17 ml/min
  - Tendency for improvement with time, 1.3 ml/min for each 10 years
- Proteinuria- marginal increase
- Blood pressure increase of 2.7 mm Hg
  - Subsequently one mm Hg up/decade
  - Incidence of hypertension - not increased
Quality of life assessment of previous kidney donors

Investigation of 478 kidney donors

Has the donation impaired your health?

<table>
<thead>
<tr>
<th>Description</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not at all</td>
<td>446</td>
<td>93.3%</td>
</tr>
<tr>
<td>A little</td>
<td>29</td>
<td>6.1%</td>
</tr>
<tr>
<td>Significantly</td>
<td>3</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

Conclusions from mortality studies

- Observed mortality is less than expected in the general population
- Observed mortality is equal to what is seen in healthy people being accepted for life insurance

Kidney donors live longer

Survival %

- Observed
- Expected

Fehrman-Ekholm et al. Transplantation 1997
Clinical work-up in aged transplant recipients

- Maximize cardiovascular investigation
- Intensive research of hidden malignancy
- Nutrition state
- Rehabilitation degree
How did it start?

Lindberg and Carrel
1935:
Normothermic, pulsatile

Future

- Better oxygen delivery: perfluorocarbons
- Long term preservation
- Reversing ischaemic damage
- Immunological manipulation
Machine preservation: pulsatile, non pulsatile and cold

- ‘Home made’
- Waters
- Organ Recovery Systems

European trial

- Less DGF after machine perfusion (70 v 89, p=0.01)
- Better 1 year graft survival after machine perfusion (94 v 90% p=0.04)
- In extension study of DCDs, DGF reduced from 70 to 54%

* Pirenne Trans Int 2009*
Kidney Transplantation in Patients with Autosomal Dominant Polycystic Kidney Disease

Mr D van Dellen
Dr D Benavente
Dr I Griveas
Dr L Foggensteiner
Specific diseases causing CGD

- Recurrent diseases
- Thrombotic microangiopathy
- BK nephropathy
- Interstitial nephritis
- De novo GN
## Risk of recurrence of IgA GN after renal transplantation

<table>
<thead>
<tr>
<th>Author</th>
<th>Pts</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berger 1988</td>
<td>32</td>
<td>17 (53%)</td>
</tr>
<tr>
<td>Schwartz 1991</td>
<td>8</td>
<td>1 (12%)</td>
</tr>
<tr>
<td>Odum 1994</td>
<td>46</td>
<td>28 (61%)</td>
</tr>
<tr>
<td>Hartung 1995</td>
<td>128</td>
<td>47 (38%)</td>
</tr>
<tr>
<td>Kessler 1996</td>
<td>28</td>
<td>13 (46%)</td>
</tr>
<tr>
<td>Klur 1996</td>
<td>75</td>
<td>36 (30%)</td>
</tr>
<tr>
<td>Frohnert 1997</td>
<td>51</td>
<td>14 (26%)</td>
</tr>
<tr>
<td>Ohmacht 1997</td>
<td>61</td>
<td>33 (61%)</td>
</tr>
<tr>
<td>Bumgardner 1998</td>
<td>61</td>
<td>18 (29%)</td>
</tr>
<tr>
<td>Freese 1999</td>
<td>104</td>
<td>13 (12%)</td>
</tr>
<tr>
<td>Hartharan 1999</td>
<td>22</td>
<td>3 (13%)</td>
</tr>
<tr>
<td>Jain 2002</td>
<td>56</td>
<td>6 (11%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>672</strong></td>
<td><strong>229 (34%)</strong></td>
</tr>
</tbody>
</table>
Recurrence of FSGS after transplantation

**Frequency** 20-30%

85-100% retransplants

**Median time** 14 days

**Presentation** Proteinuria usually nephrotic
Graft outcome in pts with recurrence of FSGS

Children  median survival 5 months
           (Erich NDT 1992)

Adults   84% lost graft function within
          32 months (1-104)
          (Hariharan AJKD 1999)
Conclusions 1

Focal and segmental glomerulosclerosis

- May recur in 20-30% of renal transplants
- Recurrence occurs early after transplantation
- Pts with recurrence have reduced graft survival
- Plasmapheresis may be helpful in several cases of recurrence

Conclusions 2

- In spite of the high risk of recurrence FSGS is not a contraindication to renal transplantation
- In case of living donation the possibility of early recurrence leading to graft loss should be clearly explained to the potential donor and recipient
Problems in defining MN recurrence

- MN is a rare cause of ESRD
- Recurrent MN and “de novo” MN are histologically indistinguishable

Recurrent MN after transplantation

<table>
<thead>
<tr>
<th>Author</th>
<th>Pts</th>
<th>Recurr.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morzycka</td>
<td>7</td>
<td>4</td>
<td>57</td>
</tr>
<tr>
<td>Berger</td>
<td>25</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Montagnino</td>
<td>9</td>
<td>3</td>
<td>33</td>
</tr>
<tr>
<td>Lustig</td>
<td>11</td>
<td>4</td>
<td>36</td>
</tr>
<tr>
<td>Couchoud</td>
<td>19</td>
<td>5</td>
<td>26</td>
</tr>
<tr>
<td>Marcen</td>
<td>6</td>
<td>3</td>
<td>50</td>
</tr>
<tr>
<td>Odorico</td>
<td>64</td>
<td>13</td>
<td>20</td>
</tr>
<tr>
<td>Cosyns</td>
<td>12</td>
<td>27?</td>
<td>25</td>
</tr>
</tbody>
</table>

Total 153 36 24%

CONCLUSIONS

- MN may recur in 20–30% of adults
- No predictive factor for recurrence is identifiable
- Spontaneous remission is rare
- Most patients progress to ESRD, but in many cases graft failure is caused by rejection rather than recurrence
Risk of recurrence in type 1 MPGN

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<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Children</strong></td>
<td>64% (Habib 1987)</td>
</tr>
<tr>
<td></td>
<td>7% (Alexander 1990)</td>
</tr>
<tr>
<td><strong>Adults</strong></td>
<td>48% (Andresdottir 1997)</td>
</tr>
<tr>
<td></td>
<td>3% (Shimizu 1998)</td>
</tr>
<tr>
<td><strong>Median time</strong></td>
<td>20 months, 1-45 (Andresdottir 1997)</td>
</tr>
</tbody>
</table>

Risk factors for recurrent MPGN 1

No risk factor has been identified
Prognosis for recurrent MPGN type 1

2-year graft survival 86%
(Briggs and Jones 1999)

Mean graft survival 40 months
(Andresdottir 1997)

Is there any effective therapy for recurrent type 1 MPGN?

Pasmapheresis
(Muczynski 1995, Saxena 2000)

Cyclophosphamide
(Lien 2000)

Anti-CMV therapy
(Andresdottir 2000)

Conclusions

- MPGN type 1 is not a contraindication to renal transplantation
- The risk for recurrence is poorly determined
- The impact of recurrence on graft survival is still unclear
Recurrence of dense deposit disease

Histological: 85-100%
Clinical: ~10%
Graft failure: 28% in children
10-13% in adults

Andresdottir (1999)
DE NOVO THROMBOTIC MICROANGIOPATHY

ETIOLOGY
Calcineurin inhibitors;
anti-mTOR agents;
OKT3

TREATMENT
Removal offending drug
Plasmapheresis
POLYOMA BK NEPHRITIS

- INCIDENCE
- 5-6%
- Reactivation BKV

- ETIOLOGY
- Decoy cells, cytopathic changes, simian virus MAB, PCR

- DIAGNOSIS
- Severe
- Reduce IS, Leflunomide

- PROGNOSIS
- TREATMENT
INTERSTITIAL NEPHRITIS

- VIRUS
  - CMV, HV 1-2, Adenovirus

- DRUGS
  - Antibiotics, Sulphonamides, Allopurinol, Diuretics, NSAID
De novo Glomerular Disease

- Membranous glomerulonephritis
- Focal glomerulosclerosis
- anti-GBM glomerulonephritis
- Membranoproliferative glomerulonephritis
- Congenital nephrotic syndrome, Finnish type
- Transplant glomerulopathy
- Thrombotic microangiopathies

Additional information:
- chronic transplant glomerulopathy
- primary
- secondary
- Alport disease
- HCV, CMV, EBV
- ab-mediated
- acute, chronic
- drugs: CsA, tacrolimus, OKT3
- virus: parvovirus, CMV, influenza A
Non specific factors of progression

- Diabetes
- Arterial hypertension
- Drug nephrotoxicity
- Proteinuria
- CMV infection
How near are we to reaching the point where transplant tolerance will become a clinical reality?
Transplantation Tolerance:
- Elements of Definition -

- Long-term acceptance of grafted tissue in absence of continuous immunosuppression

- Donor-specific immune unresponsiveness
Renal Transplantation; where to we stand today?

<table>
<thead>
<tr>
<th>FACTOR</th>
<th>OPTIMAL</th>
<th>REAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA</td>
<td>Identical</td>
<td>Mismatch</td>
</tr>
<tr>
<td>Donor source</td>
<td>Living</td>
<td>15% (2001)</td>
</tr>
<tr>
<td>Donor age</td>
<td>Young adult</td>
<td>Older and older</td>
</tr>
<tr>
<td>Recipient age</td>
<td>Young adult</td>
<td>Older and older</td>
</tr>
<tr>
<td>Anti-HLA Ab</td>
<td>Absent</td>
<td>Variable</td>
</tr>
<tr>
<td>Dialysis duration</td>
<td>No dialysis</td>
<td>Longer and longer</td>
</tr>
</tbody>
</table>
Renal Transplantation; where to we stand today?

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Renal Transplantation; where to we stand today?

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Renal Transplantation; where to we stand today?

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Factors influencing long-term outcome

**DONOR**
- age
- source
- HLA match

**RECIPIENT**
- age
- preformed Ab
- immune reactivity
- waiting time
- viral status
- specific diseases
- calcineurin-inhibitors
- factors progression
- tx glomerulopathy
- chronic rejection

**Graft Survival in Cadaveric Kidney Transplants According to Donor Age**

- 18-34
- 35-49
- 50-64
- >65

*UNOS Annual Report, 2001*
Patients with biopsy-proven recurrence of IgA after transplantation

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence</td>
<td>37/106 (35%)</td>
</tr>
<tr>
<td>Signs or symptoms of IgA GN in non biopsied patients</td>
<td>3/49 (6%)</td>
</tr>
<tr>
<td>Time at clinical diagnosis (mo)</td>
<td>46.9 ± 44.3</td>
</tr>
<tr>
<td>Time at biopsy diagnosis (mo)</td>
<td>61.7 ± 50.6</td>
</tr>
</tbody>
</table>
Predictors of FSGS recurrence

Aggressive initial course (ESRD <3yrs)
Age (less than 15 yrs)
Mesangial proliferation at biopsy

Recurrence in a previous transplant
Senggutuvan P Pediat Nephrol 4,21,1990
Tejani A JASN 2,5258,1992
Artero M Am J Med 92,375,1992
Kim M Kidney Int 45,1440, 1994
Baum M Kidney Int 59,329,2001

Circulating factor(s)

30-50 KD plasma protein bound to IgG which may be removed by plasma-exchange or by immunoabsorption by Protein A

(Savin VJ 1996, Dantal J 1998)

Risk of recurrence and permeability factor
(Dall’Amico R. et al AJKD 34,1048,1999)

Recurrence after Tx

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PF positive</td>
<td>11/13</td>
</tr>
<tr>
<td>PF negative</td>
<td>4/12</td>
</tr>
<tr>
<td>OR</td>
<td>10.99 (C.I. 1.6-75)</td>
</tr>
</tbody>
</table>
**Plasmapheresis for recurrent FSGS**

**Adults**

PD = Pheresis dependent

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artero 1994</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Dantal 1996</td>
<td>10</td>
<td>8 (8 PD)</td>
</tr>
<tr>
<td>Andresdottir 1999</td>
<td>7</td>
<td>3 (2 PD)</td>
</tr>
<tr>
<td>Osubo 1999</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td>Matalon 2001</td>
<td>13</td>
<td>4 (3 PD)</td>
</tr>
<tr>
<td>Moriconi 2001</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Ponticelli 2002</td>
<td>3</td>
<td>3 (1 PD)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>56</strong></td>
<td><strong>33 (59%)</strong></td>
</tr>
</tbody>
</table>

**The different patterns of response to plasmapheresis**

- Complete and stable remission
- Remission (complete or partial) with relapses
- Partial remission PP dependent
- No response

**Suggestions to prevent/treat FSGS recurrence**

- Pre-Tx prophylactic PP can halve the risk (Ohta 2001)
- Start PP as soon as proteinuria appears
- Post-PP cyclophosphamide may be of benefit
- High-dose ACE-i may be of benefit
- Re-start PP in case of relapse after remission
- Continue PP in PP-dependent patients
Posttransplant causes of chronic kidney graft dysfunction

- SPECIFIC DISEASES
- CALCINEURIN-INHIBITORS
- ASPERIFIC FACTORS OF PROGRESSION
- TRANSPLANT GLOMERULOPATHY
- CHRONIC REJECTION
Questions

- Is pregnancy advisable in transplant recipients?
- Will pregnancy be complicated?
- Will the baby be healthy?
- Will there be any long-term harm (mother and the baby)?

Kidney Transplantation and Pregnancy

- High-risk pregnancy
- Good prognosis:
  - 1-2 years waiting time
  - Scr<1.5 mg/dl and stable
  - Normal blood pressure (target level?)
  - No proteinuria or minimal proteinuria (level?)
  - No recent acute rejection episode
  - Low-dose prednisone (≤7.5 mg/d)
  - No recent infections especially CMV
  - Normal blood glucose level
Comorbid Factors That May Influence Pregnancy Outcome

- Etiology of original disease (recurrence?)
- Chronic allograft dysfunction
- Cardiovascular and pulmonary status
- DM or HTN
- Inherited diseases in mother or father
- Infections might affect the fetus: CMV, herpes simplex, toxoplasmosis, HBV, HCV (transmission?)
- Obesity

Potential Risks to Children Born to Transplant Recipients

- Preterm birth (14-83% vs 5-15% in general population)
- Intrauterine growth retardation (IUGR) and low birth weight (19-67% vs 5-13% in general population)
- Congenital abnormalities (no increase with CsA, chromosome aberrations with AZA)
- Adrenocortical insufficiency
- Hyperkalemia, renal dysfunction
- Immunologic abnormalities, malignancies
- Infections (CMV, hepatitis B and C, sepsis)