Renal transplantation

Karel Krejčí

3rd Internal Clinic of the Faculty Hospital and Medical Faculty of Palacký University, Olomouc
Scope of transplantation medicine

- Search for organ donors
- Organization of organ extraction
- Management of waiting list and selection of donors for transplantation
- Coordination of extractions and transplantations
- Transplantation legislation
- Surgical problems of transplantation
- Post-operative monitoring of transplant patients
- Immunosuppressive and anti-rejection therapy
- Consistent diagnostics and therapy of acute post-transplantation complications
- Background of good cooperating histopathological and immunological laboratory
- Ensuring all aspects of long-term care for transplant patients
Estimated life expectancy in hemodialysis and after renal transplantation


<table>
<thead>
<tr>
<th>Age groups</th>
<th>WL dialysis</th>
<th>Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-39</td>
<td>14</td>
<td>31</td>
</tr>
<tr>
<td>40-59</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>60-74</td>
<td>6</td>
<td>10</td>
</tr>
</tbody>
</table>
Estimated survival of 189,004 adults transplanted from 1987 to 2006

Leichtman AB.: NEJM 2007; 357: 2625-2627
Examinations before inclusion on the waiting list for renal transplantation

- Basic examination
- Basic oncological examination
- Nephrological and urological examination
- Examination of cardiovascular system
- Pulmonology examination
- Gastroenterology examination
- Psychological and psychiatric examination
- Microbiological and serological examination
Contraindications for renal transplantation

• Oncological diseases
• Chronic infections
  - Active tuberculosis
  - AIDS/HIV positive
• Severe extrarenal diseases
  - Cardiac
  - Vascular
  - Hepatic
  - Pulmonary
• Uncooperative patient
• Psycho–social problems
  - Psychoses
  - Mental handicap
  - Alcoholism
  - Drug dependence
• High age – patients above the age of 70?
Indications for temporary withdrawal from the waiting list

- Presence of acute infection
- Acute myocardial perfusion disorders
- Cardiac insufficiency
- Uremic pericarditis
- Acute CNS perfusion disorders
- Active ulcer disease
- Acute hepatitis, cholecystitis, pancreatitis
- Active urinary tract infection
- Infection of subcutaneous fistula
- Intensification of arterial hypertension
## Waiting list: Causes of chronic renal failure

*n = 518*

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cases</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>GN</td>
<td>27</td>
<td>29.3</td>
</tr>
<tr>
<td>IN/PN</td>
<td>71</td>
<td>18.5</td>
</tr>
<tr>
<td>PCL</td>
<td>54</td>
<td>12.2</td>
</tr>
<tr>
<td>HT</td>
<td>29</td>
<td>5.6</td>
</tr>
<tr>
<td>DM</td>
<td>59</td>
<td>15.1</td>
</tr>
<tr>
<td>others</td>
<td>39</td>
<td>7.5</td>
</tr>
<tr>
<td>unclear</td>
<td>61</td>
<td>11.8</td>
</tr>
<tr>
<td>IN/PN unclear</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GN+biopt.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ig A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>other cysts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADPKD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>others</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Number of cadaverous transplantations in the Czech Republic
Number of living donors transplantations in Czech Republic

- 1990: 5
- 1991: 8
- 1992: 6
- 1993: 1
- 1994: 3
- 1995: 4
- 1996: 5
- 1997: 12
- 1998: 7
- 1999: 17
- 2000: 19
- 2001: 18
- 2002: 55
- 2003: 48
- 2004: 38
- 2005: 27
- 2006: 33
- 2007: 34
- 2008: 28
- 2009: 27
- 2010: 17
- 2011: 40
Number of kidney transplantations in Faculty hospital Olomouc
Allocation of kidneys

- Urgent
- IK=0
- Child
- Special order
- Long-term waiting patients

Normal order
- 80-100% PRA, IK< 7
- 20-79% PRA, IK< 15
- 0-19% PRA, IK without limitation

RENAL BALANCE
- (indicated x transplanted)
Surgical complications after renal transplantation

- Bleeding around the graft
- Graft artery thrombosis
- Graft vein thrombosis
- Renal artery stenosis
- Urinary fistula
- Lymphocela
- Obstruction or stricture of the urinary duct
- Infection of surgical wound
Internal complications after renal transplantation

- Infectious complications
- Rejection graft impairment
- Cardiovascular diseases
- Arterial hypertension
- Hyperlipoproteinemia
- Malignities
- Osteopenia
- Avascular bone disease
- Diabetes mellitus
- Gastrointestinal complications
- Thromboembolic disease
Graft function development in Faculty Hospital Olomouc \( n = 614 \)

- Early: 52%
- Delayed: 41%
- Prim. afunction: 7%
Delayed onset of graft function

Factors of a donor
- Age of the donor
- Renal function level before extraction
- Grade of maximum diuresis
- Presence of arterial hypertension
- Cause of brain death

Factors of a recipient
- Previous transplantation
- Diuresis before transplantation

Other factors
- Duration of cold ischemia
- Quality of graft reperfusion
- Immediate post-operative diuresis
Differential diagnostics of acute graft dysfunction in the 1st week after transplantation

- Post-ischemic acute tubular nephropathy (necrosis)
- Hyperacute rejection
- Accelerated acute rejection (2nd-5th day)
- Urinary tract obstruction - compression by hematoma - urinary fistula
- Atherothrombotic graft disease (quality of vessels of the donor and recipient)
- Thrombosis of graft vessels - primary (without rejection) - secondary (within rejection)
Differential diagnostics of acute graft dysfunction in the 2nd to 12th weeks after transplantation

- Acute rejection episode
- Nephrotoxicity of calcineurine inhibitors
- Urinary tract obstruction
- Reduction of graft perfusion due to reduction of effective circulating volume
- Infectious complications (including CMV)
- Recurrence of the underlying disease
- Pharmacologically induced acute interstitial nephritis
Diagnosis of acute rejection

- Increase of plasma creatinin concentration ( > 15%)
- Reduction of diuresis
- Occasional pain in the graft, subfebrile conditions
- Typical signs in sonography of the graft
- Graft biopsy in case of unclear diagnosis
Acute kidney graft rejection

ULTRASOUND PICTURE

A. Normální UZ transplantované ledviny
B. Edém transplantované ledviny při akutní rejekci
Banff histology classification of the transplant kidney biopsy

- Normal finding
- Humoral rejection
  - C4d positivity
  - presence of donor-specific antibodies
  - typical histology signs
- Borderline changes
- Acute cellular rejection
- Chronic graft nephropathy
Acute cellular rejection

- **Type I A** - interstitial inflammation + light tubulitis
- **Type I B** - interstitial inflammation + severe tubulitis
- **Type II A** - mild arteritis (< 25% reduction of vascular lumen)
- **Type II B** - severe arteritis (> 25% reduction of vascular lumen)
- **Type III** - transmural arteritis
Acute renal graft rejection
IMMUNOHISTOCHEMISTRY


Interstitial fibrosis/tubular atrophy (previously Chronic graft nephropathy)

- Progressive reduction of the graft function (0.5 mL/min./month)
- Arterial hypertension
- Proteinuria (0.5 - 2 g/24 hr)
- Typical histological symptoms
Histopathological signs of chronic graft nephropathy

**Late vascular changes**
Rejection endarteritis
(fibrous, degenerative and transient type)

**Glomerular changes**
Recurrence of membranous glomerulopathy
Late segmental and rejection glomerulopathy
Glomerular collapse, atrophy and obliteration

**Tubulointerstitial changes**
Interstitial fibrosis
Tubular atrophy and regressive changes
Late cellular interstitial infiltration
Prevalence of chronic graft nephropathy

- Median of occurrence of chronic graft nephropathy is 3 months after kidney transplantation.

- Mild form (grade I) is present 1 year after transplantation in 94.2% of patients.
Prognostic factors of chronic rejection nephropathy

**Alloantigen dependent factors**

- Acute rejection episodes
- Grade of HLA compatibility
  (The number of HLA matches is considered as prognostically the most important factor)
- Representation of cytotoxic antibodies
  (Highly sensibilized patients - PRA >80%)
- Type of preventive immunosuppression
- Match in Rh factor
- Blood transfusion
Prognostic factors of chronic rejection nephropathy

**Alloantigen independent factors**

- Ischemic - reperfusion graft impairment
  (duration of cold ischemia, delayed onset of the function, ATN)
- Inadequate mass of transplant nephrons
  (relative to body weight of the recipient)
- Age of a donor (< 3, > 60)
- Drug non-compliance
- Post-transplant arterial hypertension
- Hyperlipoproteinemia
- Recurrence or de novo graft nephropathy
Recurrence of selected glomerulopathies after renal transplantation

<table>
<thead>
<tr>
<th>Disease</th>
<th>Histological recurrence</th>
<th>Time factor</th>
<th>Graft failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA nephropathy</td>
<td>20-70%</td>
<td>0.2-4 years</td>
<td>5-10%</td>
</tr>
<tr>
<td>MN</td>
<td>3-10%</td>
<td>10 months</td>
<td>30-50%</td>
</tr>
<tr>
<td>FSGS</td>
<td>20-50%</td>
<td>immediate &lt; 2 days early: 2-30 days late: &gt;30 days</td>
<td>40-60%</td>
</tr>
<tr>
<td>MPGN Type 1</td>
<td>20-30%</td>
<td>12 months</td>
<td>30-40%</td>
</tr>
<tr>
<td>MPGN Type 2</td>
<td>50-100%</td>
<td>1-12 months</td>
<td>10-20%</td>
</tr>
</tbody>
</table>
### Recurrence of an underlying disease after renal transplantation

<table>
<thead>
<tr>
<th>Disease</th>
<th>Histological recurrence</th>
<th>Time factor</th>
<th>Graft failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic nephropathy</td>
<td>100%</td>
<td>2-4 years</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>Lupus nephritis</td>
<td>2-9%</td>
<td>2-9.3 years</td>
<td>2-4%</td>
</tr>
<tr>
<td>Renal amyloidosis</td>
<td>20-33%</td>
<td>1.5-6 years</td>
<td>&lt; 5%</td>
</tr>
</tbody>
</table>
Current classification of immunosuppressive agents

I. Basic immunosuppressive drugs

II. Induction immunosuppressives

III. Anti-rejection immunosuppressives
# I. Basic immunosuppressive drugs

1. **Calcineurin inhibitors**
   - cyclosporine A (Sandimmun Neoral, Equoral)
   - tacrolimus (Prograf, Advagraf)

2. **Antimetabolites**
   - azathioprin (Imuran)
   - mycophenolate mofetil (Cell Cept, Myfortic)

3. **mTOR inhibitors**
   - sirolimus (Rapamune)
   - everolimus (Certican)

4. **Corticosteroids**
   - prednisone (Prednisone)
   - methylprednisolone (Medrol)
II. Induction immunosuppression

1. Antibodies against IL-2R
   - basiliximab (Simulect, Novartis)
   - daclizumab (Zenapax, Roche)

2. Polyclonal antibodies
   - antithymocytary globulin (Thymoglobuline, ATG-Fresenius)
   - antilymphocytary globulin (Lymphoglobuline)

3. Monoclonal antibodies
   - alemtuzumab (Campath-1H)

4. Monoclonal antibodies
   - muromonab
     (Cedetrin-T, Orthoclone OKT 3)
III. Anti-rejection therapy

1. **Corticosteroids**
   - methylprednisolone (Solu-Medrol)

2. **Polyclonal antibodies**
   - antithymocytary globulin (ATG-Fresenius, Thymoglobuline)
   - antilymphocytary globulin (Lymphoglobuline)

3. **Monoclonal antibodies anti - CD 20**
   - rituximab (Mabthera)

4. **Intravenous immunoglobuline**
   - (Kiovic, Endobuline)

5. **Monoclonal antibodies anti CD₃**
   - muromonab - CD3 (Cedetrin-T, Orthoclone OKT 3)
## Side effects of calcineurin inhibitors

<table>
<thead>
<tr>
<th><strong>Cyclosporine A</strong></th>
<th><strong>Tacrolimus</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Acute and chronic nephrotoxicity</td>
<td>• Acute and chronic nephrotoxicity</td>
</tr>
<tr>
<td>• Increase of BP</td>
<td>• Diabetes mellitus</td>
</tr>
<tr>
<td>• Hyperlipidemia</td>
<td>• Neurotoxicity (tremor)</td>
</tr>
<tr>
<td>• Hirsutism</td>
<td>• Smaller increase of BP</td>
</tr>
<tr>
<td>• Gingival hyperplasia</td>
<td>• Milder hyperlipidemia</td>
</tr>
<tr>
<td>• Hemolytic-uremic syndrome</td>
<td>• Hirsutism and gingival hyperplasia are not present</td>
</tr>
</tbody>
</table>
Gigival hyperplasia after cyclosporin
Individualization of immunosuppressive therapy

Goals

- Reduction of incidence of acute rejection
- Improvement of long-term graft function
- Improvement of long-term survival of patients
Long-term monitoring of a renal graft recipient

- Monitoring the function of a transplanted kidney
- Prevention, prophylaxis and therapy of infectious complications
- Diagnosis and therapy of cardiovascular complications
- Detection of oncological diseases
- Diagnosis and therapy of metabolic complications
- Diagnosis and therapy of hematological disorders
Cardiovascular diseases are the most frequent cause of death with functional graft

USRDS 1st kidney transplants 1994-2000 (n= 67,874)

- Cardiovascular diseases: 39.6%
- Infection: 24%
- Neoplasms: 9.3%
- Others: 27.1%
Risk factors for cardiovascular diseases in transplant recipients

Risk factors for atherosclerosis in transplant recipients The risk factors for cardiovascular disease found in the transplant recipient include hyperlipidemia, hypertension, diabetes mellitus, hyperhomocysteinemia, uremia, and others (shown in blue). Many of these factors are exacerbated by the immunosuppressive drugs (shown in green) in current clinical use to prevent rejection.

Ducloux D et al.: Kidney Int., 2004
Hyperlipidemia after renal transplantation

- Hypercholesterolemia > 5.2 mmol/L 80 - 90%
- LDL cholesterol > 2.6 mmol/L 90 - 97%
- Hypertriacylglycerolemia > 2.1 mmol/L 30 - 40%

Kasiske B et al.: Am J. Transplant, 2004
Causes of hyperlipidemia after renal transplantation

- Immunosuppressive drugs
  - corticosteroids
  - calcineurin inhibitors
  - sirolimus, everolimus
- Diabetes mellitus
- Obesity
- Nephrotic syndrome
- Hypothyrosis
- Alcohol abuse
- Chronic liver disease
Transplantation and malignity

- Post-transplant malignancies are currently the third most common cause of morbidity and mortality in long-term transplant patients.
- The main causes of malignities are the suppression of cellular immunity (T cells and NK cells) and viral co-factors (EBV, HPV, HHV, CMV).
- The type and duration of immunosuppression have a significant influence.
- Occurrence of solid tumors and lymphomas in a transplant recipient who undergoes immunosuppressive therapy is 2 times and 4.3 times higher, respectively, compared to the rest of the population.

<table>
<thead>
<tr>
<th>Risk of cancer:</th>
<th>Transplant population vs. General population</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild Risk</strong></td>
<td>Colon, lung, prostate, gastric, esophagus, pancreas, ovarium and breast</td>
<td>2</td>
</tr>
<tr>
<td><strong>Moderate Risk</strong></td>
<td>Testes and urinary bladder</td>
<td>3</td>
</tr>
<tr>
<td><strong>High Risk</strong></td>
<td>Cutaneous melanoma, leukemia, liver and gynaecological tumors</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Renal</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Kaposi Sarcoma, PTLD, Skin cancer</td>
<td>&gt;20</td>
</tr>
</tbody>
</table>

Post-transplant diabetes mellitus

- Increase of morbidity and mortality of transplant individuals
- Worsening of graft function
- Shortening of graft survival
- Worsening of quality of life
Corticosteroids and development of diabetes after renal transplantation

The diabetogenic effect of corticosteroids depends on their dose and duration of administration. An increase of daily dose of steroids by 0.01 mg/kg is associated with 4% increase of the risk of glucose intolerance and 5% increase of the risk of manifestation of diabetes mellitus.

Calcineurin inhibitors and post-transplant diabetes mellitus

• Reduction of insulin secretion
  - reduction of C peptide
  - reduction of insulinemia

• Increase of insulin resistance
  - reduction of insulin/glucose ratio

Glukocorticoids affect mainly insulin resistance while calcineurin inhibitors (tacrolimus) reduce mainly insulin secretion

Effects of calcineurin inhibitors on β cells depends on the dose and is reversible
Calcineurin inhibitors and diabetes mellitus

Meta-analysis:

Insulin dependent diabetes mellitus appeared in 11.5% of patients with a transplanted kidney treated with tacrolimus and in 4.7% of patients treated with cyclosporine A.

Heisel O et. al.: Am J Transplant, 2004
Post-transplant bone disease

Incidence

Osteopenia, osteoporosis 28-88%
Avascular bone necrosis 3%
Syndrome of symmetrical bone pain 11%

Sperschneider H et al.: NDT, 2003
Glucocorticoids and bone

• **Reduction of bone production**
  - direct inhibition of osteoblasts
  - inhibition of IGF – 1 production
  - reduction of testosterone production
  - increase of apoptosis of the osteoblasts and osteoclasts

• **Increase of bone resorption**
  - reduction of androgen and estrogen production via inhibition of gonadotropine secretion
  - increase of PTH secretion as a result of reduction of absorption of Ca from the GIT and increased elimination of Ca in kidneys

The effects of glucocorticoids on bone are proportional to their dose and duration of therapy.
Causes of persistent anemia in post-transplant period

• Insufficient development of graft function
• Iron deficiency
• Immunosuppressive therapy
  - bone marrow suppression
    (azathioprin, MMF, MPA, sirolimus)
  - hemolytic-uremic syndrom
    (calcineurin inhibitors, sirolimus)
• Other drugs
  (also ACE, AT1 blockers, trimetoprin)
• Viral infections
  (CMV, EB virus, herpes virus 6, parvovirus B19)
Hyperuricaemia and gout after renal transplantation

**Incidence of hyperuricaemia:** 30-84%

**Incidence of gout:** 7-24%

**Pathogenesis:** Reduction of glomerular filtration

Impairment of tubular functions (urate secretion)

**Therapy:**

- **Allopurinol** (cave interference with 6-merkaptopurin metabolism)
- **Losartan** (↑ fraction excretion of UA by 17% and ↓ of uricemia by 8%)
- **Uricosurics** (normal graft function, absence of lithiasis)
- **NSAIDs** (cave reduction of glomerular filtration)
- **Colchicin** (calcineurin inhibitors reduce clearance of colchicin)
- Transient increase of corticosteroid dose

*Clive DM.: J Am Soc Nephrol, 2000*