Kidney Transplantation

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Current Kidney Transplantation


Worldwide Transplant Directory

<table>
<thead>
<tr>
<th>Organ</th>
<th>Centers</th>
<th>2002</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>578</td>
<td>28,298</td>
<td>585,877</td>
</tr>
<tr>
<td>Kidney-Pancreas</td>
<td>161</td>
<td>1,111</td>
<td>14,161</td>
</tr>
<tr>
<td>Pancreas</td>
<td>113</td>
<td>622</td>
<td>4,917</td>
</tr>
<tr>
<td>Liver</td>
<td>237</td>
<td>9,579</td>
<td>112,153</td>
</tr>
<tr>
<td>Heart</td>
<td>233</td>
<td>3,267</td>
<td>66,559</td>
</tr>
<tr>
<td>Lung</td>
<td>117</td>
<td>1,661</td>
<td>15,490</td>
</tr>
<tr>
<td>Stem Cell</td>
<td>280</td>
<td>8,987</td>
<td>136,635</td>
</tr>
</tbody>
</table>

*No report of failure or death

Cecka, Clinical Transplants 2002 (p.2)
Current Kidney Transplantation

Shortage of donor ➞ Living donor > Cadaveric donor

Change of graft survival rate
Change of graft survival rate

Improvement of survival rate and half-life

Short-term survival  Long-term survival
Comparison between dialysis and transplantation

### Quality of Life

<table>
<thead>
<tr>
<th></th>
<th>Dialysis</th>
<th>Kidney Transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Functional social activity recovery rate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal social activity</td>
<td>59%</td>
<td>44%</td>
</tr>
<tr>
<td>Normal, sometimes assist</td>
<td>25%</td>
<td>25%</td>
</tr>
<tr>
<td>Self care only</td>
<td>9%</td>
<td>13%</td>
</tr>
<tr>
<td>Need assistance</td>
<td>7%</td>
<td>18%</td>
</tr>
<tr>
<td><strong>Quality of life</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Machine-dependent</td>
<td>4-8 times/2-3 times/week</td>
<td>Life-long medication</td>
</tr>
<tr>
<td><strong>Quality of health</strong></td>
<td>Only 20% of normal renal function</td>
<td>Near normal value</td>
</tr>
<tr>
<td>Hgb: 7.0-8.0 / Hct: 20 – 22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUN: 60 - 80 / Cr.: 6.0-8.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electrolyte imbalance(+)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding tendency(+)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Only 20% of normal renal function
Screening procedures for kidney transplantation

- Recipient
- Donor
- Matching degree of HLA
- Lymphocyte crossmatching
- Exclusion criteria
  Screening procedure
- Kidney transplantation

HLA typing

- Major Histocompatibility Complex in human
- Class I: HLA-A, B, C
  Direct presentation, cytotoxic T-cell activation
- Class II: HLA-DP, DQ, DR
  Indirect presentation, Helper T-cell activation
- Located in Chromosome No. 6 short arm
- Mendelian heritage pattern
Graft survival rate according to degree of HLA match
- Cadaveric donor kidney transplantation

Graft survival rate according to degree of HLA match
- Living donor kidney transplantation
Lymphocyte Cross Matching

- Performed antibodies in recipient’s serum
- Hyperacute rejection
- Type
  - T cell: Modified and Johnson’s method
  - B cell: Warm (37°C) and Cold (4°C)
- PRA (Panel Reactive Antibody): screening test for sensitization to the common antigen

Hyperacute rejection
very rapid onset
Humoral immunologic = vessel involved
Granulocyte massive infiltration with vasculitis combined hemorrhage
Tx: Graft nephrectomy
Contraindication for Transplantation

- Disseminated Malignancy
- Infection, unresponsive to treatment
- Refractory cardiac failure or respiratory failure
- Progressive hepatic failure
- Severe mental retardation
- Severe congenital urinary tract abnormality
- Extensive vascular disease

Recurred disease after kidney transplantation

- Diabetes: 100% but recurred late
- FSGS: 30-70% with nephrotic syndrome
- IgA nephropathy: 50% occasional graft failure
- MPGN type 2: > 90% slow graft failure
- Oxalosis: 90%
- HUS (Hemolytic uremic syndrome)
- Amyloidosis, Cystinosis, Fabry’s, Anti-GBM nephritis
Graft survival rates according to original kidney disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Five-Year Survival (%)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerulonephritis</td>
<td>60.3</td>
<td>13,992</td>
</tr>
<tr>
<td>Diabetes</td>
<td>57.7</td>
<td>12,682</td>
</tr>
<tr>
<td>Hypertensive Nephrosclerosis</td>
<td>52.0</td>
<td>7,544</td>
</tr>
<tr>
<td>Polycystic Kidney Disease</td>
<td>67.7</td>
<td>4,860</td>
</tr>
<tr>
<td>Nephritis / Nephropathy</td>
<td>63.9</td>
<td>3,972</td>
</tr>
<tr>
<td>Systemic Lupus Erythematosus</td>
<td>59.1</td>
<td>1,572</td>
</tr>
</tbody>
</table>


Screening Procedure for Recipients

- Active infection or malignancy
- Adequate cardiopulmonary function
- VCUG
- UGI or EGD
- U/S
- Liver function test with viral marker study
- Others - Dental and ENT evaluation
Normal VCUG

Filling phase | Post-voiding phase

Point of view
Bladder contour?
VUR?
Residual urine?

VCUG
- Grade III/IV VUR = indication of native nephrectomy
Evaluation process for potential living donors - Donor screening

- Educate patient regarding cadaveric and live related donation
- Take family history and screen for potential donors
- Review ABO compatibilities of potential donors
- Tissue-type and crossmatch ABO compatible potential donors
- Choose primary potential donor with patient and family
- Educate donor regarding process of evaluation and donation

Potential advantages of living kidney donation

1. Better short-term results
   (approximately 95% versus 80% 1-yr function)
2. Better long-term results (half-life of 12-20 yr versus 7-8yr)
3. More consistent early function and ease of management
4. Avoidance of long wait for cadaveric transplant
5. Capacity to time transplant for medical & personal convenience
6. Immunosuppressive regime may be less aggressive
7. Helps relieve stress on national cadaver donor supply
8. Emotional gain to donor
Potential disadvantages of living kidney donation

1. Psychological stress to donor and family
2. Inconvenience and risk of evaluation process (i.e., IVP and angiogram)
3. Operative mortality (approximately 1/2000)
4. Major postoperative complications (approximately 2%)
5. Minor post-operative complications (up to 50%)
6. Long-term morbidity (possibly mild hypertension and proteinuria)
7. Risk of traumatic injury to remaining kidney

Contraindications to cadaveric donation

<table>
<thead>
<tr>
<th>Absolute</th>
<th>Relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 70</td>
<td>Age &gt; 60</td>
</tr>
<tr>
<td>Chronic renal disease</td>
<td>Age &lt; 6</td>
</tr>
<tr>
<td>Potentially metastasizing malignancy</td>
<td>Mild hypertension</td>
</tr>
<tr>
<td>Severe hypertension</td>
<td>Treated infection</td>
</tr>
<tr>
<td>Bacterial sepsis</td>
<td>Donor ATN</td>
</tr>
<tr>
<td>Intravenous drug abuse</td>
<td>Donor medical disease</td>
</tr>
<tr>
<td>Positive HBsAg or anti-HCV*</td>
<td>(diabetes, SLE)</td>
</tr>
<tr>
<td>Positive HIV</td>
<td>Prolonged cold ischemia</td>
</tr>
<tr>
<td>Intestinal perforation</td>
<td></td>
</tr>
<tr>
<td>Prolonged warm ischemia</td>
<td></td>
</tr>
</tbody>
</table>

ATN = acute tubular necrosis, HCV = hepatitis C virus, HIV = human immunodeficiency virus, SLE = systemic lupus erythematosus
Exclusion criteria for living donors

Current trend, donor

- Inferior survival rate
- Donor shortage
Evaluation process for potential living donors - Donor evaluation

Noninvasive
- Complete history and physical examination
- Comprehensive laboratory screening to include
  - CBC, chemisry panel, HIV, VDRI, HBsAg, anti-HCV, CMV, GTT
    (for diabetic families)
  - Urinalysis, urine culture, pregnancy test
    - 24-hr urine collection for protein (twice)
    - 24-hr urine collection for creatinine (twice), Ccr.
- Chest x-ray, cardiogram, exercise treadmill for patients over age 50
- Intravenous pyelogram, Ultrasonography
- Psychiatric evaluation

Invasive
- Renal angiogram

Normal Renal Angiogram
Renal artery stenosis

Two renal artery

Unilateral small kidney
Rt.: 1 Artery 1 Vein
Lt.: 2 Artery 1 Vein

Rt. double ureter & pelvis
Surgery of kidney transplantation

- Incision
  - Extraperitoneal vs. Transperitoneal approach
- Anastomosis of artery
  - End-to-end vs. End-to-side anastomosis
- Ureteral anastomosis
  - Ureteroneocystostomy vs. Pyeloureterostomy

Alexis Carrel (1873-1944)
OP. Procedure (1)  
-- Op. field exposure

Hockey-Stick incision

External iliac vein
External iliac artery

OP. Procedure (2)  
-- Vessel dissection

External iliac artery
External iliac vein
OP. Procedure (3)
-- Vein Anastomosis

OP. Procedure (4)
-- Arterial Anastomosis
End-to-End
OP. Procedure (4)
-- Arterial Anastomosis
End-to-Side

OP. Procedure (5)
-- Ureteroneocystostomy
Operative Technique

renal artery - Internal iliac artery
end-to-end anastomosis

renal artery - Internal iliac artery
end-to-side anastomosis

Operative Technique

Two renal artery

Pediatric kidney transplantation
Intra-peritoneal approach
Indications of native nephrectomy

- Uncontrolled hypertension esp. renal origin
- VUR Grade > III and refractory UTI
- Large sized polycystic kidney
- Persistent or recurrent pyelonephritis
- Nephrostomy in place
- Heavy proteinuria with edema
Post-transplant Management

<table>
<thead>
<tr>
<th>I. Fluid therapy</th>
<th>half saline with/without glucose with sodium bicarbonate / potassium tapering for 1-2 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>II. Systemic antibiotics</td>
<td>avoid nephrotoxic drug prophylactics for bacterial infection</td>
</tr>
<tr>
<td>III. Anti-acid</td>
<td>prophylactics for peptic ulcer</td>
</tr>
<tr>
<td>IV. Trimethoprim /sulfamethoxazole</td>
<td>prophylactics for urinary tract infection and pneumocystis carinii</td>
</tr>
<tr>
<td>V. nystatin, oral</td>
<td>prophylactics for fungal infection</td>
</tr>
<tr>
<td>VI. Hypertension control</td>
<td>hydralazine, beta-blocker, calcium-channel blocker, ACE-inhibitor</td>
</tr>
<tr>
<td>VII. Stitch out</td>
<td>post-operative 2-3 weeks</td>
</tr>
<tr>
<td>VIII. Foley catheter</td>
<td>protection of ureteroneocystostomy for 1-7 days</td>
</tr>
<tr>
<td>IX. Diet</td>
<td>no limitation after gas passing (retroperitoneal approach)</td>
</tr>
</tbody>
</table>

Immunosuppressive Regimens

<table>
<thead>
<tr>
<th>Double</th>
<th>CsA+Steroid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triple</td>
<td>CsA+Steroid+AZA/MMF</td>
</tr>
<tr>
<td>Quadruple</td>
<td>CsA+Steroid+AZA/MMF +anti-lymphocyte Ab.(OKT3,ATG)</td>
</tr>
<tr>
<td>Living donor KTx</td>
<td>Cadaveric KTx or Immediate post-Tx ATN</td>
</tr>
</tbody>
</table>
Induction Immunosuppression

MMF 1.5-2.0 g/day or AZA 1-2 mg/kg/day

General Characteristics of Cyclosporine (Sandimmune®; Neoral®)

**Clinical Use**
- Prophylaxis of rejection with corticosteroids, with or without azathioprine or mycophenolate mofetil; with or without antilymphocyte induction (ABG or monoclonal CD3)

**Mechanism**
- Inhibits IL-2 production; T cell proliferation

**Dose**
- 0.5-5 mg/kg IV constant infusion over 24 hours to achieve whole blood trough levels measured by monochrom TDX (diuresis, renal function, administered). 200-400 ng/ml in the immediate postoperative period (see below). Start with cyclosporine 2.5-7.5 mg/kg/day, once GI function has been regained. Patients able to take the drug by NG tube or mouth and/or when T tubes are clamped to avoid nephrotoxicity due to prolonged exposure to IV cyclosporine. Conversion from IV to oral requires a threshold increase in oral dose. Adjust dose by adding or subtracting 25% of the previous total daily dose in 25 mg/kg increments (based on trough level, toxicity, liver function).

**Levels**
- Days Post-Transplant
- Cyclosporine (ng/ml), whole blood trough levels (monoclon)
  - 0-30: 200-400
  - 31-90: 200-450
  - 91-180: 150-250
  - >180: 50-350

**Adverse Effects**
- Nephrotoxicity, increased BUN, SCr, K+, CNS/Neurotoxicity: nightmares, depression, fatigue, anxiety, headache, paresthesias, tremor, confusion, altered level of consciousness, Central Pontine Myelolysis (transaminitis with dose reduction); hyperkalemia; hyperchloremic acidosis; gastrointestinal; MAVIDA (if excessive diathermy, may require IV C172 since oral absorption is reduced); hypokalemia (4%); first month dose related; bone marrow toxicity (rare): leukopenia, anemia, thrombocytopenia; other adverse effects: insolation, hypercalcemia (5%), hypertriglyceridemia, hyperuricemia, hyperglycemia, hyperparathyroidism, hypertension, PFTD (1.3%)

**Drugs that Increase or Decrease Cyclosporine**
- (See Table 42-5)

**Pharmacodynamic Drug Interactions**
- Amphotericin B, dexamethasone, nitrofurantoin, epinephrine, dopamine, alprostadil, doxorubicin, vincristine, inhibits the P450 intestinal membrane of brush border
Immunosuppressive agents

General Characteristics of Tacrolimus (Prograf®; FK506)

**Clinical Use**
- Prophylaxis of rejection with corticosteroids, with or without azathioprine or MMF; with or without antilymphocyte induction

**Mechanism**
- Inhibits IL-2 production; T cell proliferation

**Dose**
- Adults: 0.015-0.05 mg/kg q 12 h iv (given as a continuous infusion or 0.05-0.1 mg/kg q 12 h p.o. to maintain whole blood trough levels of 5-15 ng/ml (see below)
- Pediatric: 0.05-0.075 mg/kg q 12 h (constant infusion) and 0.15 mg/kg p.o. q 12 h
- Intravenous administration is not routine; start tacrolimus p.o. (as above) 12-24 hours post-transplant in adult or pediatric patients (ng/ml)

**Levels**
- Postoperative day <30: 5-15 mg/m²; postoperative day 31-90: 5-10 mg/m²; postoperative day >91: 5 mg/m² (whole blood trough levels)
- Higher doses may be required in pediatric patients (increased tacrolimus clearance); lower doses may be required in the elderly, or those with reduced liver function (reduced tacrolimus clearance). If toxic, reduce the dose and maintain a lower serum level (i.e., <5 ng/ml). Adjust dose by adding or subtracting 20% of the previous total daily dose in 1-5 mg increments (based on trough level, toxicity, liver function).

**Adverse Effects**
- Nephrotoxicity: increased BUN, SCr, K+, p-NDA, Hb, total bilirubin, renal dysfunction, polyuria, polydipsia, hypokalemia, hypocalcemia, hypomagnesemia, rashes, pruritus, anaphylactic reactions; pleural effusions; bone marrow suppression (myelosuppression, immune thrombocytopenia, anemia); peritonitis; glucose intolerance (diabetes); Other: alopecia, arthralgias, increased cholesterol synthesis (less than COX), hypertension, post-transplant lymphoproliferative disease (PTLD) in pediatric patients.

**Drugs that increase or decrease Tacrolimus**
- (See Table 40-6)

**Pharmacokinetic Drug Interactions**
- Amphotericin B, cyclosporine, RAL/NSAIDs, enhanced nephrotoxicity; TMP-SMX: TMP may interfere with the tubular secretion of creatinine or interfere with the assay for SCr; does not lower GFR.

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General Characteristics of Mycophenolate Mofetil (Cellcept®; RS61443)

**Clinical Use**
- Used for treatment and prevention of acute and steroid-resistant rejection in renal transplant patients
- Will be evaluated in liver and heart allograft recipients for prevention of acute rejection
- Replaces azathioprine in cyclosporine-based immunosuppressive regimens
- Not routinely used with tacrolimus-based immunosuppressive regimens, but may be used to minimize or avoid adverse effects due to tacrolimus (nephrotoxicity, neurotoxicity)

**Mechanism**
- Hydrazido-N-sulfonated mycophenic acid (MPA), the active immunosuppressive, which is a potent and specific inhibitor of de novo purine synthesis. Inhibits inosine monophosphate dehydrogenase (IMPDH). MPA has a selective inhibitory effect on T- and B-lymphocytes (cell and humoral mediated immunity) proliferation.

**Dose**
- 1.0 grams p.o. b.i.d. (range 1-2 g p.o. b.i.d.; no guidelines for serum level monitoring at this time)

**Adverse Effects**
- Gastrointestinal (mild): nausea, vomiting, abdominal pain, diarrhea, and loss of appetite
- Gastrointestinal (severe): gastric ulceration, gastritis, GI bleeding, jaundice, and pancreatitis
- Neutropenia, acidosis (rare)
- Other: dermatologic (rash), infection (CMV), lymphoma, 7 teratogenicity

**Pharmacokinetic Drug Interactions**
- Few data on clinically significant pharmacokinetic drug interactions

**Pharmacodynamic Interactions**
- Sulfonolamines, thalidomide, methotrexate may have additive bone marrow suppressive effects
Causes of polyuria after transplantation

- Ishemic injury of graft kidney = mild ATN

Hypervolemic status
- ineffective dialysis
- volume expander during operation

Hyperosmolar status
- elevated BUN/cr.
- Colloid fluid infusion during operation

Immediate/early post-transplant oliguria
Cause of renal-origin oliguria

1. Delayed graft function
   ; Acute tubular necrosis (ATN)

2. Cyclosporine nephrotoxicity

3. Acute rejection

Delayed Graft Dysfunction,
Post-transplant Acute Tubular Necrosis

Definition: serum creatinine level > 2.5 mg% at POD #15
   or need dialysis within POD # 7

Risk factors: (1) prolonged cold ischemic time ( > 24 hours)
   (2) prolonged anastomosis time ( > 40 mins.)
   (3) donor age

Diagnosis: Doppler, Renogram, Graft biopsy

Treatment:
   1. Avoid nephrotoxic agents - especially cyclosporine
   2. Prevention of acute rejection
   3. Supportive management - Anemia correction,
      maintain of fluid and electrolyte balance

“Sequential Quadruple immunosuppression”
Sequential Quadruple immunosuppression

Avoidance of cyclosporine nephrotoxicity
Prevention of acute rejection

Cyclosporine nephrotoxicity

Clinical manifestation
increment of serum-cr. : less than acute rejection
fluctuation of serum-cr. by whole blood CsA level
reversal of serum-cr. after reduction of CsA dosage

Definitive diagnostic study = graft kidney biopsy
; arteriosclerosis
Rejection versus CsA nephrotoxicity

Acute rejection

Diagnosis

Rapid onset (within 6 months)
Typical clinical symptoms
uncommon in CsA-treated group
closed monitoring of s-cr.
Graft biopsy is definitive diagnostic study
Acute rejection

Incidence
- within post-transplant 6 months
- rare after post-transplant 1 year
  “delayed acute rejection” = acute rejection occurred after 1 year

Graft biopsy findings
- Parenchyme, small vessel involved
- Cellular >> Humoral immunologic response
- Mononuclear mixed cell inflammation
- Interstitial edema and hemorrhage
- Tubulitis
Acute rejection

Anti-rejection therapy - timing of diagnosis $\propto$ response rate
avoid prolonged or over-treatment

<table>
<thead>
<tr>
<th>Immunosuppressive regimens used in the treatment of rejection</th>
</tr>
</thead>
</table>
| pulse therapy  
intravenous methylprednisolone or prednisolone  
(0.5–1.0 g daily for 3 days)  
oral prednisone (3 mg/kg daily for 5 days with slow taper) |
| antilymphocyte globulin  
intravenous polyclonal ALG (15–30 mg/kg daily for 7–14 days)  
intravenous monoclonal OKT, (5 mg daily for 7–14 days) |
| cyclosporine  
oral (5–10 mg/kg) |

Chronic rejection = Chronic graft dysfunction

Definition

After 6 months, slowly deterioration of graft function
characteristic pathologic findings
I. Transplant glomerulopathy
II. Interstitial fibrosis
III. Tubular atrophy and arterial intimal fibrosis

Rescue therapy
MMF, FK-506
Chronic rejection = Chronic graft dysfunction

Pathogenesis

Immunologic causes

1. Endothelial cell injury
2. Release cytokines
3. Proliferation of vascular smooth muscle cell
4. Migration of vascular smooth muscle cell
5. Proliferative obstructive vasculopathy
6. Glomerulosclerosis / mesangial cell proliferation
7. Ischemic injury

Non-immunologic cause

Risk factors affecting chronic allograft nephropathy

Immunologic factors
- Poor HLA matching and previous sensitization
- Delayed graft function
- Episodes of acute rejection
- Subacute and chronic alloimmune response
- Noncompliance of patient
- Suboptimal immunosuppression

Nonimmunologic factors
- Older donor or poor graft quality
- Brain-death injury, preservation injury, or ischemic injury
- Acute peritransplantational injuries
- Delayed graft function
- Hyperpertension
- Hyperlipidemia
- Chronic toxic effects of cyclosporine or tacrolimus

Pascual M et al. NEJM 2002; 346: 580
Chronic rejection = Chronic graft dysfunction

Immunologic factors

I. Immunologic injury = acute rejection episodes
   pro: related with acute rejection history
      especially multiple
      and delayed onset rejection (> 3 months)

   con: lowering acute rejection ≠ chronic rejection

II. Histocompatibility differences

Non-immunologic factors

I. Ischemia/Reperfusion injury
II. Infection
cytomegalovirus (CMV) infection
III. Immunosuppressive agents
cyclosporine/FK-506 - focal glomerulosclerosis
IV. Lipid abnormalities
   hyperlipidemia, triglycerides, hypercholesterolemia
V. Hyperfiltration = relatively small numbers of nephron
   donor-recipient size mismatching
   ex) gender, BMI difference, kidney weight/recipient weight
VI. Hypertension
Chronic rejection = Chronic graft dysfunction

Prevention
I. Avoid acute rejection & acute rejection sequale
II. Avoid under immunosuppression
III. Prevention and Early management Infection
IV. Control Hypertension, Hypercholesterolemia, Hyperglycemia
V. Maintain Ideal body weight

Treatment
New immunosuppressive agent – MMF, Rapamycin
Agent for smooth muscle cell – dilatrend

→ effect is not confirmed !!!!!

Diagnostic Tool

Doppler; Resistant Index

\[
RI = \frac{PSV - DV}{PSV}
\]

- Normal : 0.58 +/- 0.12
- Acute rejection: 0.78 +/- 0.14
- ATN, Infection: 0.70 +/- 0.05
Doppler; Resistant Index

Pre-treatment
R.I. = 0.825

Post-treatment
R.I. = 0.665

Renogram; nuclear renal scan

Normal

Rejection/ATN
Diagnostic Tool

Renogram; nuclear renal scan

- ATN
- Post-op, normal range

Diagnostic Tool

Graft kidney biopsy

Indications

1. Increased serum creatinine level, > 25% of basal creatinine
2. Proteinuria (> 1g/day)
3. Microscopic hematuria (relative indication)

Pathologic classification

- Acute rejection
- Chronic rejection
- Glomerulonephritis - recurred or de novo
  IgA nephritis, FSGS, MPGN, RPGN
- Cyclosporine toxicity
- others
Graft kidney biopsy

Definitive diagnostic study

1. Classification of pathology
2. Grade of pathology
3. Combined pathology

Graft survival rate by biopsy results:
Chronic rejection & CsA toxicity

Prognosis of chronic rejection:
A. according to the pathology
B. according to the clinical status
Post-transplant Complications

- ATN
- Rejection
- CsA toxicity
- Vascular complication
- Urologic complication
- Immunosuppression
  - Infection & malignancy
  - Recurred & de novo

Immunsuppression related complication


<table>
<thead>
<tr>
<th></th>
<th>With Function</th>
<th></th>
<th>After Graft Loss</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>annual rate %</td>
<td>N</td>
<td>annual rate %</td>
</tr>
<tr>
<td>Overall</td>
<td>10,816</td>
<td>2.81</td>
<td>4,712</td>
<td>9.42</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>3,402</td>
<td>0.69</td>
<td>2,252</td>
<td>4.31</td>
</tr>
<tr>
<td>Infectious</td>
<td>1,856</td>
<td>0.37</td>
<td>879</td>
<td>1.63</td>
</tr>
<tr>
<td>Malignancy</td>
<td>808</td>
<td>0.19</td>
<td>122</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Calculated from a Cox model adjusted for 20 covariates
### Major Side Effects of immunosuppression

**Dependent on the “net state of immunosuppression”**

<table>
<thead>
<tr>
<th>Infection: atypical infection</th>
<th>Malignancy: viral origin cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>virus: CMV, HSV, HCV, VZV, EBV, HIV,</td>
<td>hematologic: PTLD</td>
</tr>
<tr>
<td>fungus: cryptococcus, candidiasis</td>
<td>lymphoma</td>
</tr>
<tr>
<td>mycobacteria: atypical M.</td>
<td>skin cancer</td>
</tr>
<tr>
<td>Etc.: pneumocystis carinii</td>
<td>urogenital: cervix cancer</td>
</tr>
<tr>
<td></td>
<td>bladder cancer</td>
</tr>
<tr>
<td></td>
<td>Etc.: Kaposi’s sarcoma</td>
</tr>
</tbody>
</table>

**Drug-related side effects**

### Varicella-zoster virus infection
CMV pneumonitis
- CMV IgM(+) x4
- CMV-PCR (+)
- Inclusion body

CMV enteritis
- Inclusion body(+)

Inclusion body(+)
Mycobacterial Infection
- relatively common atypical mycobacteria
- extra-pulmonary involvement

Prevalence & Types of Tuberculosis

<table>
<thead>
<tr>
<th>Type of Tuberculosis</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td>28</td>
</tr>
<tr>
<td>pleurisy</td>
<td>9</td>
</tr>
<tr>
<td>miliary</td>
<td>6</td>
</tr>
<tr>
<td>Extrapulmonary</td>
<td></td>
</tr>
<tr>
<td>intestine</td>
<td>3</td>
</tr>
<tr>
<td>bone</td>
<td>2</td>
</tr>
<tr>
<td>soft tissue</td>
<td>1</td>
</tr>
<tr>
<td>CNS</td>
<td>1</td>
</tr>
<tr>
<td>intestine + soft tissue</td>
<td>1</td>
</tr>
<tr>
<td>pulmonary + spine</td>
<td>2</td>
</tr>
<tr>
<td>tonsill</td>
<td>11 (21.2%)</td>
</tr>
</tbody>
</table>

Spinal Tbc.
Intestinal Tbc.
Soft tissue Tbc.
Duodenal Tbc.
Fungal Infection

- Esophageal candidiasis

Karposi’s sarcoma

- Neck mass
- Lung metastasis
Cyclosporine-related side effects

s-Cr.
K+
Total Bilirubin > SGOT/PT
Cholesterol
Uric acid
Glucose

Neurologic – tremor
Hypertension
Hypertrichosis
Gum hyperplasia

Urologic complication – VUR via neoureterocystostomy
### Longest Surviving Transplants - 2002

<table>
<thead>
<tr>
<th>Organ Type</th>
<th>Surv yrs</th>
<th>Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIDNEY Related don</td>
<td>40</td>
<td>University of Colorado</td>
</tr>
<tr>
<td>KIDNEY Cadaver don</td>
<td>37</td>
<td>University of Minnesota</td>
</tr>
<tr>
<td>KIDNEY Unrelated living</td>
<td>31</td>
<td>FMUSP-Sao Paulo</td>
</tr>
<tr>
<td>LIVER</td>
<td>33</td>
<td>University of Colorado</td>
</tr>
<tr>
<td>HEART</td>
<td>24</td>
<td>Stanford University</td>
</tr>
<tr>
<td>PANCREAS-KIDNEY</td>
<td>21</td>
<td>Univ Hosp-Zurich</td>
</tr>
<tr>
<td>PANCREAS</td>
<td>19</td>
<td>University of Minnesota</td>
</tr>
<tr>
<td>LUNG</td>
<td>15</td>
<td>The Toronto Hospital</td>
</tr>
<tr>
<td>BONE MARROW</td>
<td>30</td>
<td>FHCRC-Seattle</td>
</tr>
</tbody>
</table>
Results of Kidney Transplantation

- Graft survival rate
- Patient survival rate
- Half-life ($t_{1/2}$)
- Functional graft survival rate (death-censored)

Definition of graft fail

- Graft nephrectomy
- Convert to dialysis
- Patient death

with graft fail
without graft fail (=functioning graft)

Improvement in Cadaver Donor Kidney Survival Results

Cecka, Clinical Transplants 2002 (p.2)
Improvement in Living Donor Kidney Survival Results

Risk factors affecting graft survival rate

- Immunologic
- non-immunologic

- HLA matching
- PRA score
- Type of immunosuppression
- Acute rejection history
- Delayed graft function
- Donor type (living vs. cadaver)
- Recipient age
- Race of recipient
- Preemptive transplant
- Donor age
- Ischemic time
- Donor medical illness (DM, hypertension)
- Recipient medical illness (DM, HBV, hypertension)
- Donor-recipient size mismatching
- Recurrent original kidney disease

Cecka, Clinical Transplants 2002 (p.13)
Effect of HLA match on Graft Survival Rate
USRDS 2001
Graft survival rate by HLA Mismatching

Effect of HLA matching on Graft Survival Rate

UNOS 1997  YUMC 1996
Effect of HLA matching on Graft Survival Rate
in Living related donor transplantation

Effect of HLA Mismatches on Early Rejection Episodes (1998-2001)

Cecka, Clinical Transplants 2002
Effect of Acute rejection on Graft Survival Rate

USRDS 2001
Graft survival rate by Donor age
Effect of Donor age on Graft Survival Rate

<table>
<thead>
<tr>
<th>Donor Age</th>
<th>Five-Year Survival (%)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>57.4</td>
<td>216</td>
</tr>
<tr>
<td>1-5</td>
<td>55.1</td>
<td>1,826</td>
</tr>
<tr>
<td>6-10</td>
<td>56.0</td>
<td>2,226</td>
</tr>
<tr>
<td>11-17</td>
<td>63.3</td>
<td>8,124</td>
</tr>
<tr>
<td>18-34</td>
<td>63.9</td>
<td>21,059</td>
</tr>
<tr>
<td>35-49</td>
<td>57.1</td>
<td>12,838</td>
</tr>
<tr>
<td>50-64</td>
<td>49.4</td>
<td>7,919</td>
</tr>
<tr>
<td>65+</td>
<td>40.3</td>
<td>1,071</td>
</tr>
</tbody>
</table>


USRDS 2001

Graft survival rate by Recipient age
**Preemptive Transplant**

= Transplant without regular dialysis

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### Graft Survival Rates for Preemptive Transplants and Effect of Dialysis Time

*Nishikawa, Clinical Transplants 2002 (p.374)*

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### Delayed Graft Function Rates According to Pretransplant Duration of Dialysis

*Nishikawa, Clinical Transplants 2002 (p.372)*
USRDS 2001
Graft survival rate by Cold ischemia time in cadaveric transplants
Thank You

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