Patients Selection for Kidney Transplantation

All patients with ESRD are candidates for KT unless

- Systemic malignancy.
- Chronic infection.
- Severe cardiovascular disease.
- Neuropsychiatric disorder.
- Extremes of age (relative).

Patient Survival after Kidney Transplantation VS haemodialysis

- Annual mortality rates for patients under dialysis range from 21%-25%, but <8% with cadaveric and <4% with living-related transplant recepients.
- Healthier patients generally are selected for transplantation.
- The benefit of transplantation is most notable in young people and in those with diabetes mellitus.

Projected years of life for patients 20-39 years old:

<table>
<thead>
<tr>
<th></th>
<th>Dialysis</th>
<th>Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non diabetic</td>
<td>20</td>
<td>31 years</td>
</tr>
<tr>
<td>Diabetic</td>
<td>8</td>
<td>25 years</td>
</tr>
</tbody>
</table>

Kidney Donor

- Living related.
- Living unrelated (emotionally motivated).
- Cadaveric (Brain-dead)

Beating and non-beating heart.

CRITERIA FOR LIVING DONOR SELECTION

- Blood relative.
- Highly motivated.
- ABO blood group-compatible.
- HLA-identical or haploidentical with negative cross-match.
- Excellent medical condition with normal renal function.
CRITERIA FOR CADAVER DONOR SELECTION

- Irreversible brain damage.
- Normal renal function appropriate for age.
- No evidence of preexisting renal disease.
- No evidence of transmissible diseases.
- ABO blood group-compatible.
- Negative cross-match.
- Best HLA match possible, particularly at the DR and B loci.

Principles Involved In evaluating A Prospective Living Kidney Donor

- Whether there is a medical condition that will put donor at increased risk for complications for general anaesthesia or surgery.
- Wether the removal of one kidney will increase the donor’s risk for developing renal insufficiency.

Evaluation Of Kidney Function In Potential Kidney Donor

- Serum creatinine.
- Creatinine clearance.
- Radionuclide glomerular filtration rate.
- Urine analysis.
- Urine Culture.
- GFR > 70 ml/min.

Medical Conditions That Exclude Living Kidney Donation

- Renal parenchymal disease.
- Conditions that may predispose to renal disease
  
  History of stone disease
  History of frequent UTI
  Hypertension
  D.M.
- Conditions that increase the risks of anaesthesia and surgery.
Recent malignancy.

Does Donation Of A kidney pose a long-term Risk for the Donor?

- Following nephrectomy, compensatory hypertrophy and increase in GFR occur in the remaining kidney.
- Slight risk of proteinuria and hypertension.
- Meta-analysis of data from donors followed for >20y confirmed safety of kidney donation.

CONTRAINDICATIONS TO RENAL TRANSPLANTATION

- ABO incompatibility.
- Cystoxic antibodies against HLA antigens of donor.
- Recent or metastatic malignancy.
- Active infection.
- AIDS.
- Severe extrarenal disease (cardiac, pulmonary, hepatic).
- Active vasculitis or glomeulonephritis.
- Uncorrectable lower urinary tract disease.
- Noncompliance.
- Psychiatric illness including alcoholism and drug addiction.
- Morbid obesity.
- Age > 70 years.
- Primary oxalosis.
- Persistent coagulation disorder.

Matching between Recipient And Donor

A- Tissue typing

- Determined by 6 antigens located on cell surface encoded for by the HLA gen located on the short arm of chromosom 6.
- Class I antigens (HLA-A and HLA-B) are expressed on the surface of most nucleated cells.
- Class II antigen (HLA-DR) are expressed on surface of APC and activated lymphocytes.
- These 6 antigens are refered to as major transplant antigens.
- The match between donor and recepient can range from 0 to six.

B- Cross matching

- A laboratory test that determines weather a potential transplant recepient has preformed antibodies against the HLA antigens of the potential donor. (Donor Lymphocytest +Recepient Serum)
- A Final CM is mandatory

C- Compatible ABO blood group.
Effect Of HLA Matching On The Graft Outcome

- Data from large registries indicate that, the better the HLA-match, the better the long-term survival of the allograft.
- The benefits of matching are particularly noteworthy in recipients of kidneys from donors with zero mismatch.
- The benefits of lesser degrees of matching have become less obvious with the use of newer and more potent immunosuppressive drugs.
- Matching for DR antigens are more favorable than others.

The beneficial effect of HLA B and DR matching in patients with and without the benefit of cyclosporine.

Factors Influencing the Longevity of Renal Allograft

- Age
- HLA matching
- Delayed graft function
- Ischemia time.
- Number of acute rejection episodes.
- Native kidney disease.
- Ethnicity.
- Others

Relative incidence of causes of allograft dysfunction during the year following transplantation.

What Are The Major Causes Of Long-Term Allograft Failure?

- Chronic rejection.
- Death with functioning graft.

What Are The Most Common causes Of Death After Kidney Transplantation?

- Cardiovascular disease.
- Infection.
Contraindications To Renal Transplantation

Absolute:
- Severe vascular disease.

Relative:
- Recent malignancy.
- Coronary artery disease.
- Active bacterial, fungal, or viral disease.
- HIV positivity.
- Social conditions.
- Others.

Renal Allograft Rejection

1- Hyperacute.
2- Acute.
3- Chronic.

Hyperacute Rejection
- Is mediated by preformed antibodies that recognize HLA antigens in donor organ.
- Usually these are formed as a consequence of blood transfusion, pregnancy, prior organ transplantation, autoimmune diseases.
- Fibrinoid necrosis lead to immediate graft loss.
- Delayed form may occur several days following transplantation.
- Plasmapheresis and pulse steroid may be used.

Acute Renal Allograft Rejection
- Is mediated by activated T-lymphocytes.
- Activations of T-cells occur after recognition of graft antigen either directly or after being processed and presented by APC.
- This usually occur during the first 6 mon.
- It manifest as increase in s. creatinine with or without oliguria.

How Common Is acute Rejection?
- At least one episode of acute rejection occurs in 62% in patients treated by CsA, Aza and steroids.
- With Newer immunosuppressants drugs rates are less.
  - CSA, Aza, Steroid+Simulet is 36%
  - ST, Rapa+ (MM For FK) + Simulect is ~ 18%
Treatment of Acute Rejection

1. Pulse steroids
2. ATG, OKT3.
3. MMF, Tacrolimus.
4. IVIG.

More than 90% of acute rejection episodes occurring in the first 6 mon can be reversed.

Chronic allograft Rejection

- Manifest clinically by a slow and gradual decline in renal function, usually more than 6 mon after transplant and typically accompanied by moderate to heavy proteinuria.

- Histologically, characterized by glomerulo-sclerosis, interstitial fibrosis, and obliteration of arteriolar lumina.

- Treatment is unsatisfactory.

Chronic allograft Rejection VS Transplant glomerulopathy

- A- Immunologic
- B- Non-immunologic
  - hypertension
  - Hyperlipidemia
  - Drug toxicity (CsA, FK)
  - Ischaemic injury
  - Viral infection (CMV)
  - Others

- C4d deposits in peritubular capillaries as marker of ongoing immune injury

Management of Transplant glomerulopathy

- Switch from calcineurin inhibitor.
- ACEIs or ARBs.
- Statins.
- Increasing immunosuppression?
- Others
**Banff criteria for diagnosis of allograft rejection**

<table>
<thead>
<tr>
<th>BANFF GRADE</th>
<th>HISTOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Interstitial edema and tubulitis (i.e. lymphocytic invasion of tubular basement membranes.)</td>
</tr>
<tr>
<td>II</td>
<td>More severe tubulitis with or without mild vasculitis characterized by intimal lymphocytic infiltrates</td>
</tr>
<tr>
<td>III</td>
<td>Severe vasculitis with fibrinoid necrosis</td>
</tr>
</tbody>
</table>

**Principles underlying current immunosuppressive treatment**

1- The benefits of a successful transplant outweight the risks of chronic immunosuppression.

2- Immunosuppressive therapy is required indefinitely.

3- Multidrug regimens are generally employed.

4- Large doses of immunosuppressant drugs are used in the early transplant period.

**Classes of Maintenance Immunosuppressive Drugs**

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunophilin-binding agents</td>
<td><strong>Calcineurin inhibitors</strong></td>
</tr>
<tr>
<td></td>
<td>Cyclosporine</td>
</tr>
<tr>
<td></td>
<td>Tacrolimus (FK506)</td>
</tr>
<tr>
<td></td>
<td><strong>Calcineurin-independent agents</strong></td>
</tr>
<tr>
<td></td>
<td>Sirolimus (rapamycin)</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td><strong>Purine inhibitors: nonselective</strong></td>
</tr>
<tr>
<td></td>
<td>Azathioprine</td>
</tr>
<tr>
<td>Antimetabolites</td>
<td><strong>Purine inhibitors: lymphocyte selective</strong></td>
</tr>
<tr>
<td></td>
<td>Mycophenolate mofetil (RS-61443)</td>
</tr>
<tr>
<td></td>
<td>Mizoribine*</td>
</tr>
<tr>
<td></td>
<td><strong>Pyrimidine inhibitors</strong></td>
</tr>
<tr>
<td></td>
<td>Brequinar*</td>
</tr>
<tr>
<td>Poorly understood mechanisms</td>
<td><strong>Deoxyspergualin</strong></td>
</tr>
<tr>
<td></td>
<td>Leflunomide*</td>
</tr>
</tbody>
</table>

*Experimental or not yet approved by Food and Drug Administration (FDA)
Risks associated with chronic Immunosuppression

- 1- Malignancy
- 2- Infection
- 3- Side effects of different drugs (steroids, CsA, tacrolimus, MMF, .....

Side Effects of Glucocorticoids

- Weight gain with cushingoid features
- Hypertension
- Hyperlipidemia
- Osteopenia
- Cataracts

- Dermatologic effects (acne, striae, easy bruisingability, impaired wound healing)

Side Effects of Immunophiline-binding Agents

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Cyclosporine</th>
<th>Tacrolimus</th>
<th>Sirolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrotoxicity</td>
<td>++</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Neurotoxicity (tremor, seizures)</td>
<td>+</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Gingival hyperplasia</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hypertension</td>
<td>++</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>++</td>
<td>+/-</td>
<td>+++</td>
</tr>
<tr>
<td>Glucose intolerance</td>
<td>+</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>Bone marrow suppression</td>
<td>-</td>
<td>-</td>
<td>++</td>
</tr>
</tbody>
</table>

Side Effects of Antimetabolites

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Azathioprine</th>
<th>Mycophenolate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mofetil</td>
<td></td>
</tr>
<tr>
<td>Bone marrow suppression</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>
Induction Immunosuppressive therapy

- During the first 1-3 weeks post transplant.
- Usually refer to use of anti-T-cell antibodies
  - Polyclonal (ATGAM, thymoglobin).
  - Monoclonal (Simulect, Zinapax, OKT3).
- Helpful to delay use of calcineurin drugs, may decrease acute rejection and improve graft outcome (debatable).
- Expensive, risk of infection and malignancy
- Better used in selected patients.

### Side Effects of Induction Antibodies

<table>
<thead>
<tr>
<th>Side effect</th>
<th>OKT3</th>
<th>Polyclonal</th>
<th>Anti-CD25 Agets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>+++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Headache</td>
<td>++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Myalgias</td>
<td>++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(diarrhea, nausea)</td>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>+</td>
<td>+/-</td>
<td>-</td>
</tr>
</tbody>
</table>

Some commonly used combinations of maintenance Immunosuppressive drugs

1- Prednisolon + Azathiaprine
2- Prednisolon + cyclosporine (or tacrolimus)
3- Prednisolon + cyclosporine + Azathioprine
4- MMF (cell cept) may replace Azathioprine.
5- Sirolimus (Rapimmune) may replace Azathioprine or cyclospine

**Common drug interactions**

- Drugs acting on cytochrome P<sub>450</sub> affect the metabolism of CsA, tacrolimus, and sirolimus.
  1- ↑ Metabolism ————↓ level
     • Anticonvulsants
     • Antituberculous
  2- ↓ Metabolism ————↑ level
     • anti-fungus (ketoconazole..)
- Erythromycin and clarithromycin
- Calcium channel blockers
- Metoclopramide
- Azathioprine and allopurinol.

In general, renal transplantation should be recommended as the preferred mode of RRT for most patients with ESRD in whom surgery and subsequent IS is safe and feasible.

- Cr CI 50-100 ml/min.
- Anaemia.
- Conception and childbearing.
- Growth in children.
- Bone metabolism.
- Work rehabilitation.

Note:

Please have a look at the ppt file.