INTRODUCTION:
The first renal transplantation was successfully performed at the Brigham and Bent hospital in the year 1954. Renal transplantation is the commonest transplantation that is performed all over the world. Today there are isolated reports of renal transplantation being performed even on HIV infected patients and patients with hepatitis B and C infection in the absence of significant liver disease.

RENAI TRANSPANTATION, THE INDIAN SCENARIO
In India the first renal transplantation was performed at the Christian Medical College, Vellore in the year 1971. Today in India 170 institutions are recognized for kidney transplantation, with approximately 3,500 transplantations performed every year. Though this looks like a large number there are a large number of ESRD patients who are yet to receive transplantation. There are nearly 150 ESRD patients per million population, but among them only 3.5 receive transplantation every year. Deceased donor transplantation rate in India is 0.08 per million population. Poisoned organ donors: cobra bite brain dead victims (recipient still alive 13 years with good functioning graft) and organophosphorus poisoning brain death victims and others have been successfully used as organ donors. Diabetics with ESRD and elderly in their seventies are also accepted for transplantation provided they have no serious co-morbid conditions like coronary artery disease, malignancy etc. The manufacture of generic immunosuppressive drugs by the Indian pharmaceutical companies has greatly decreased the cost of immunosuppression. A lack of registry of Indian transplant recipients makes it difficult to analyze graft and patient survival over time. The major cause of graft failure in India is due to non-compliance to immunosuppressive drugs usually due to economic constraints. Infection and cardiovascular related deaths are the major causes of mortality in the Indian transplant recipients. In Christian Medical College, Vellore they have introduced a novel method of increasing donors called donor swapping. By this method if a recipient has a donor who is HLA incompatible, this donor can donate to another recipient who is compatible with his HLA haplotype. In return the first recipient will receive a graft from the donor of the second recipient.

WHAT IS NEW IN RENAL TRANSPLANT IN INDIA

BASICS ABOUT TRANSPLANTATION
Organs that can be transplanted
Organs such as lung, heart, kidney, liver, pancreas, intestine, stomach, skin, islets of Langerhans, bone marrow, cornea, bone, and heart valves are the commonly transplanted organs of which the commonest to be transplanted is the kidney.

Types of transplants
- **Autograft:** Transplant of tissues to the same person, e.g.: skin grafts, vein extraction for coronary artery bypass grafting
- **Allograft:** An allograft is a transplant of an organ or tissue between two genetically non-identical members of the same species.
- **Isograft:** A subset of allografts in which organs or tissues are transplanted from a donor to a genetically identical recipient (such as an identical twin).
- **Xenograft and xenotransplantation:** A transplant of organs or tissue from one species to another.
- **Split transplants:** Sometimes a deceased-donor organ, usually a liver, may be divided between two recipients, especially an adult and a child.
- **Living donor transplant:** The graft is taken from a donor who is alive.
- **Deceased donor transplant:** Here the graft is obtained from a donor who is dead. This is of 2 types namely: heart beating and non heart beating. The chilling of a tissue or organ during decreased blood perfusion or in the absence of blood supply is commonly employed to prevent graft necrosis. Cold ischemia time during organ transplantation begins when the organ is cooled with a cold perfusion solution after organ procurement surgery, and ends after the tissue reaches physiological temperature during implantation procedures. Warm ischemia time starts then and ends with completion of surgical anastomosis. The usual accepted cold ischemia time for the kidney is 21 ± 7 hours. However the
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more prolonged the cold ischemia time the poorer is the graft survival [1].

What is HLA matching

HLA denotes human leukocyte antigen. They are proteins found on the surfaces of white blood cells and the other tissues in the body. They are expressed on the sixth chromosome. There are 3 general groups of HLA. HLA- A, HLA- B, and HLA- DR. There are many different HLA proteins within each of these 3 groups e.g. There are 59 different HLA-A proteins, 118 different HLA-B proteins and 127 different HLA-DR proteins. The term “haplotype” means a combination of all these 3 HLA proteins (eg: in Figure 1, in the father the numbers 1,8,10 represents HLA-A1, HLA-B8 and HLA-DR10 and this combination of 3 HLA proteins is called a haplotype). In Figure 1 we can see how a child inherits one HLA in each group. If 2 children inherit the very same HLA from their parents they are an HLA ‘identical match’ (Figure 2). While another child in the same family can inherit different combination of HLA (Figure 3).

Here (Figure 3) the two children do not match at all in their HLA. You inherit one haplotype from each parent. Therefore, there are a total of four different haplotype combinations from 2 parents. There is a basic rule in HLA inheritance. The rule is: you have a 25% chance of inheriting all of the same HLA (same 2 haplotypes) as any one of your siblings, you have a 25% chance of not inheriting any of the same HLA (none of the same haplotypes) and you have a 50% chance of sharing 1 haplotype with your siblings. Therefore, you have a 1 in 4 chance of being an identical match with your siblings. After HLA is determined, there is a second test which will indicate if there is specific immune reactivity between the donor and recipient. This test is the “cross match”. The cross match is a test which determines if the recipient has antibody to the potential donor. The cross match is performed by mixing a very small amount of the patient's serum with a very small amount of the potential donor's white cells in the presence of complement and the test is called complement dependent cytotoxicity. If the patient has antibody to the donor's HLA, the donor's cells will be injured and this is referred to as a “positive cross match”. A current and historical positive cross match is a contraindication for a transplant between the same donor and the recipient, since it signifies that the patient has the ability to attack the donor's cells, and would most likely attack the donor's transplanted kidney. The reasons for a positive cross match are blood transfusions, prior transplantations and/or pregnancies. A negative cross match indicates that the patient does not have HLA antibody against that particular donor, and a transplant can be performed. PRA (Percent Reactive Antibody) is the amount of HLA antibody present in a patient's serum. The PRA is determined by testing the patient's serum to a panel of 60 different types of HLA. If, for example, the patient's serum reacts with 30 out of 60 HLA, then the patient's PRA is 50% (1/2 of 60). The PRA is calculated for each monthly serum sample. In addition to determining how much or how little PRA a patient has, we need to know how specific the antibody is. That is, is the antibody specific to a particular HLA? For example, if you received a transfusion from a donor with HLA-A2, you may develop antibody to A2. That's antibody specificity. Some patients have one or two antibody specificities, while others have numerous specificities. We are able to determine the specificity at
the same time which we test for the monthly PRA. Therefore, the monthly PRA gives us two very important pieces of information about the patient’s serum, how much or how little antibody is present, HLA antibody specificity.

### ABO blood group antigens and Kidney Transplantation

<table>
<thead>
<tr>
<th>Donor</th>
<th>Recipient</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>identical</td>
</tr>
<tr>
<td>B</td>
<td>Mismatched</td>
</tr>
<tr>
<td>AB</td>
<td>Mismatched</td>
</tr>
<tr>
<td>O</td>
<td>compatible</td>
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</table>

Identical: no reaction; Mismatched: recipient antibodies cause Hyperacute rejection; Compatible: Donor cells produce antibodies to recipient cells, though the reaction is not severe.

**How to stratify patients according to their immunological risk**

<table>
<thead>
<tr>
<th>Level of risk</th>
<th>Factors involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>000 or favourable mismatch&lt;br&gt;No anti-HLA antibodies&lt;br&gt;Age under 60 years</td>
</tr>
<tr>
<td>Medium risk</td>
<td>2 or more mismatches&lt;br&gt;Anti-HLA antibodies&lt;br&gt;2nd Kidney transplant&lt;br&gt;Age over 60 years</td>
</tr>
<tr>
<td>High risk</td>
<td>Unmatched donor and recipient&lt;br&gt;Serum reactivity to mismatched donor HLA</td>
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### Immunosuppression for each level of risk

<table>
<thead>
<tr>
<th>Level of risk</th>
<th>Factors involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>Prednisolone 0.33 mg/kg body weight&lt;br&gt;Tacrolimus 0.1 – 0.2 mg/kg body weight&lt;br&gt;Basiliximab</td>
</tr>
<tr>
<td>Medium risk</td>
<td>Prednisolone&lt;br&gt;Tacrolimus&lt;br&gt;Mycophenolate Mofetil 1g twice a day&lt;br&gt;Basiliximab</td>
</tr>
<tr>
<td>High risk</td>
<td>As above but anti-thymocyte globulin for first 10 days then commence MMF</td>
</tr>
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### Classification of drugs used for immunosuppressive therapy: (Refer figure 4)

<table>
<thead>
<tr>
<th>S. No</th>
<th>Drugs</th>
<th>Mechanism of action</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Corticosteroids</td>
<td>Blocks phospholipase A2</td>
<td>Peptic ulcers, osteoporosis, cushingoid features, Infections, congestive cardiac failure, insomnia, myopathy, cataract, glaucoma, obesity, hypertension, atherosclerosis, Hypercholesterolemia</td>
</tr>
<tr>
<td>2</td>
<td>Calcineurin inhibitors</td>
<td>Inhibits calcineurin phosphate and blocks T cell activation</td>
<td>Nephrotoxicity, hypertension, post transplant diabetes mellitus, neurotoxicity, hemolytic uremic syndrome</td>
</tr>
</tbody>
</table>

1. Cyclosporine
2. Tacrolimus
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s.

no
drugs Mechanism of action side effects
b. Tacrolimus (FK 506) Binds to FKBP12 and Inhibits calcineurin phosphate and blocks T cell activation Similar to cyclosporine but higher incidence for post transplant diabetes mellitus, and neurotoxicity Hyperlipidemia, thrombocytopenia, delayed wound healing.
c. Sirolimus (rapamycin) Binds to FKBP12, inhibits IL-2 induced T cell activation.
d. Everolimus

3 Inhibitors of nucleotide synthesis
a. Mycophenolate Mofetil Blocks purine synthesis and prevents T and B cell proliferation Gastrointestinal symptoms, leucopenia, thrombocytopenia

4 Antimetabolites
a. Azathioprine Inhibits DNA synthesis Bone marrow depression, Liver toxicity

5 Protein drugs
a. Polyclonal antithymocyte globulin Blocks T cell membrane proteins CD2, CD3, CD45 Cytokine release syndrome (fever, chills, hypotension), thrombocytopenia, leucopenia, serum sickness
b. Muromonab CD3 Binds to CD3 associated T cell receptors Cytokine release syndrome, pulmonary edema, acute renal failure Infusion reactions and hypersensitivity

c. Rituximab Binds to CD20 receptors on B cells and lyses them

d. Basiliximab Binds to CD25 receptors of T cells, chimeric mab

Using therapeutic drug monitoring immunosuppressive medications dosage can be tailored for cyclosporine A, tacrolimus, sirolimus and everolimus. Pharmacokinetic monitoring is very important in the early part of transplantation to monitor drug toxicity and to avoid rejections.

Complications of over-immunosuppression
1. Reactivation of latent tuberculosis.
2. Cytomegalovirus infection
3. Pneumocystis pneumonia
4. BK virus nephropathy
5. Kaposi sarcoma
6. Squamous cell carcinoma
7. New Onset Diabetes After Transplantation (NODAT)
8. Osteoporotic bone fracture
9. Hyperlipidemia and anemia

PREGNANCY, THE KIDNEY AND TRANSPLANTATION
What are the renal changes that happen during pregnancy?
1. Kidney volume increases by 30%
2. Effective renal perfusion increases by 50 to 80% due to reduced renal vascular resistance
3. GFR increases by 30 to 40% by 13th week
4. Serum creatinine drops by 0.4 to 0.5 mg/dl, hence normal value for serum creatinine during pregnancy is 0.46 +/- 0.13 mg/dl, BUN: 8.7 +/- 1.5 mg/dl, uric acid: 2.5 - 4
5. Serum sodium decreases by 5 meq/l

What are the risks of transplantation during pregnancy?

Risks to mother | Risks to the fetus | Risk to the graft
--- | --- | ---
Spontaneous abortions | Preterm birth (< 37 wk) | Rejection difficult to diagnose: S.Cr falls during pregnancy
50% Mean gestational age – 34 wk
Hypertension and increased pre-eclampsia – 15-30% as compared to 5%

Low birth weight (<2500g)

Increased risk of irreversible graft loss if pre-pregnancy Cr > 1.5 mg/dl and proteinuria > 500 mg/24 hr

Gestational diabetes

IUGR

Developmental delays

Anemia

Autoimmune disorders

Urinary tract infections -42%

CMV infection

Congenital structural abnormalities

Caesarean Section

Immunosuppressive medications use in pregnancy

1. Steroids- associated with Intra Uterine Growth Retardation (IUGR), PROM (Premature Rupture of Membranes); safe in lower dose

2. Cyclosporine – can cause HTN, there may be a fall in drug levels during pregnancy

3. MMF and tacrolimus – first trimester pregnancy loss

4. Avoid MMF and Rapamycin for 6 wks before pregnancy and throught pregnancy

What are recommendations of transplantation during pregnancy?

1. Preferable to wait >/= 1 year following LDRT & >/= 2 years following CRT to avoid rejection-related complications (drug doses are lower & doses are stable)

2. Graft should preferably be functioning well (stable Cr < 1.5 mg/dl, proteinuria < 500mg/d)

3. Frequent monitoring

4. Aggressive treatment of hypertension (goal is normalization of BP)

5. Close monitoring for preeclampsia

6. Evidence suggests that pregnancy is not an immunosuppressed state & transplant medications should not be reduced based on that notion

7. Encourage vaginal delivery, in case caesarian section is necessary, obstetrician should know graft and ureter location

8. Careful wound closure & prophylactic antibiotics to avoid infection

9. Contraception: theoretical problems with hormonal methods, IUDs less effective & increased risk of infection, barrier methods traditionally preferred

10. Biopsy after 32 weeks is not recommended (? if applies to transplant patients?).

REFERENCES:


5. John P Vella, Gabriel Danovitch Nephsp January 2008; 7: 1