Overview of Renal Transplantation

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Associate Professor of Medicine
Objectives

- History of transplantation
- Incidence and prevalence of ESRD
- “Renal Transplant” the Optimal Choice for ESRD
- Immunosuppression therapy and outcomes
- Barriers / Limitations in renal transplantation
- Future of Renal transplantation
The History of Transplantation

- Hindu’s god of wisdom, Ganesh
- The minotaur in Greek mythology
- The Egyptian Gods bearing heads of animals
The Patron Saints of Transplantation

Saints Cosmos and Damian, identical twin physicians in the 4th century AD

Their most miraculous surgery was transplantation of the lower extremity of a dead Ethiopian gladiator to a custodian of a Roman basilica (gangrenous leg)
Imagination to Reality - Early 20th Century

- **1902 - Prof. Ullmann:** 1st Experimental kidney transplant in a Dog
- **1933 - Prof. Voronoy:** 1st Human-to-human kidney transplantation
- **1933-1944:** Six additional transplants performed – all failed
- **A successful Kidney Transplant would require:**
  - Medical support for Kidney failure (Dialysis, HTN)
  - Blood group and tissue “Matching”
  - Preservation of the donor kidney
  - Overcoming the immunologic barrier
The First Successful Kidney Transplant

December 23, 1954 at Brigham Hospital by Dr. Joseph Murray between Herrick brothers (Monozygotic twins)
The experimental, risky, limited treatment option 50 yrs ago, Has become  a routine clinical practice in > 80 countries

~ 17,000

~ 170,000
Victim of its Own Success: Wait List

Kidney Transplant is considered the major advancement of modern medicine

>92,000 patients are waiting for about 12,000 deceased donor kidneys available each year
Demand-Supply Crisis

- **Number of new patients added to the waiting list:**
  - > 30,000 patients are added to the list each year

- **Death rate on the waiting List:** ~8%
  - > 4500 patients waiting for kidney transplant die each Year

- **Number of deceased donors available remains unchanged:**
  - > 12,000 potential organ donors/year
  - < Less than 50% of them become actual donors.
INCIDENCE AND PREVALENCE OF ESRD
The incidence of ESRD in 2010 ~ 120,000
The Prevalence of ESRD~ 600,000
ESRD on therapy has increased 10 fold in 30 yrs
Global Burden of ESRD

March 8th is the “World kidney day”
MODALITY OF THERAPY OF ESRD

Renal replacement therapy
Most new patients begin therapy on hemodialysis.

- 2% Transplant
- 7% Peritoneal dialysis
- 91% Hemodialysis

And in the entire ESRD population, 3 in 10 patients have a kidney transplant.

Incident ESRD patients

30% Transplant
65% Hemodialysis
5% Peritoneal dialysis

Prevalent ESRD patients

While most hemodialysis occurs in a dialysis unit, use of home hemodialysis is rising. In Australia and New Zealand, 9–18% of dialysis patients receive therapy at home.
Transplant – The Optimal Choice

Alonzo Mourning

Restores Health to near Normal in most Patient
Renal Transplantation

“The Optimal Choice”

Renal Transplantation

- Long term survival: Better
- Quality of life: Better
- Cost-effective: $12000 vs. $60,000 (Tx vs. HD)
Renal Transplant: Survival Benefits

<table>
<thead>
<tr>
<th>Age</th>
<th>Without Transplant</th>
<th>With Transplant</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-19</td>
<td>26 y</td>
<td>39 y</td>
<td>13 y</td>
</tr>
<tr>
<td>20-39</td>
<td>14y</td>
<td>31y</td>
<td>17y</td>
</tr>
<tr>
<td>40-59</td>
<td>11y</td>
<td>22y</td>
<td>11y</td>
</tr>
<tr>
<td>60-74</td>
<td>6y</td>
<td>10y</td>
<td>4y</td>
</tr>
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</table>

Wolfe RA et al, NEJM 1999;341:1725
Comparison of Mortality: Transplant vs. Dialysis

Annual death rate: 2.6 x
Patients on dialysis vs. waiting for a transplant

Annual death rate: 1.7 x
Patients on the wait list vs. transplant recipients

NEJM, 341:1725, 1730, 1999
Economic Benefits

• Cost of therapy:
  - Annual cost of hemodialysis: $60,000-$80,000
  - Cost of transplant during first year ~$120,000
  - Thereafter: $10,000-12,000 per year.
Transplantation: Quality-of-Life Benefits

- Relatively unrestricted diet
- Freedom to travel
- Restoration of fertility (in some)
- Return to Employment
- Lifestyle free of dialysis constraints
Immunosuppression and Outcomes in Transplantation
1. **Induction immunosuppression**
   Intense IS during and immediately after Tx

2. **Maintenance immunosuppression**
   Two or three drug regimen as long as the allograft functions

3. **Treatment of Rejection**
   Immunosuppression for rejection (ACR and AMR)

4. **Tolerance Regimen - still a dream**
   Selective unresponsiveness to donor antigen
Immunosuppression: Most commonly used

**Induction**
- Thymo or Campath (T-cell depleting)
- Simulect
- IL2-RA & T-cell depleting

**Maintenance**
- None
- With steroids
- Steroid-free
- All others
- Cyclo + MMF/MPA
- None reported
- TAC + MMF/MPA
# LUMC Immunosuppression Protocol
## Recipient Risk Profile

<table>
<thead>
<tr>
<th>DEFINITION</th>
<th>INDUCTION</th>
<th>MAINTENANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low Risk</strong></td>
<td></td>
<td></td>
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</tbody>
</table>
| • 1<sup>st</sup> transplant  
• PRA <20%  
• Non-AA &  
• <3 HLA mismatches | Basiliximab 20 mg IV – days 0 and 4  
AND  
Methylprednisolone 500 mg IV | • Start Tacrolimus 0.05 mg/kg q12h when SrCr ↓ by 50% from baseline or serum creatinine < 4 mg/dL  
• Myfortic 720 mg bid  
• Prednisone |
| OR | | |
| Kidney transplant in a pt with a functioning non-renal transplant | ON CALL TO OR:  
Myfortic 720 mg x 1 | |

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<tbody>
<tr>
<td>POD 1</td>
<td>Methypred 250 mg</td>
</tr>
<tr>
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<td>Methypred 125 mg</td>
</tr>
<tr>
<td>POD 3</td>
<td>Methypred 60 mg</td>
</tr>
<tr>
<td>POD 4</td>
<td>Prednisone 15 mg daily</td>
</tr>
<tr>
<td>POD 14</td>
<td>Prednisone 10 mg daily</td>
</tr>
<tr>
<td>POD 21</td>
<td>Prednisone 5 mg daily</td>
</tr>
</tbody>
</table>

| **High Risk** | | |
| • Current or Historic PRA > 20%  
• African Americans  
• Re-transplant  
• Anticipated CIT >24h  
• DSA positive  
• OR surgeon discretion  
• DGF risk ↑  
• DR HLA mismatch | Thymoglobulin  
1.5 mg/kg/day x 4 doses  
AND  
Methylprednisolone 500 mg IV | • Start Tacrolimus 0.05 mg/kg q12h (50% for DGF)  
• Myfortic 720 mg bid  
• Prednisone |

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</table>
Mechanisms of Action

Antigen Presenting Cell

Signal 1

Signal 2

Steroids

Signal 3

Interleukin-2

Anti-IL-2R

Belatacept

B7

MHC II

OKT3

ATG

CD45

CD4

CD3

CD28

TCR

Calcineurin Pathway

Cyclosporine & Tacrolimus

Steroids

Cytokine gene

nucleus

T Lymphocyte

TOR Pathway

Sirolimus

MMF

Cell Cycle

Target lymphocyte

Purine Synthesis
Immunosuppression: Vigilance

• **Monitor for:**
  - Drug toxicities
  - Drug Interactions
  - Over Immunosuppression – infection and malignancy
  - Under Immunosuppression - Rejection
Monitor for Drug Toxicities

**CSA**
- Nephrotoxicity
- Neurotoxicity
- Hypertension
- Hyperlipidemia
- Hirsutism

**Steroids**
- Osteoporosis
- Weight gain
- Hyperglycemia
- Body changes
- Others

**Tacrolimus**
- Nephrotoxicity
- Neurotoxicity
- Hypertension
- Hyperglycemia
- GI toxicity

**MMF**
- Cytopenias
- GI toxicity

**Sirolimus**
- Hyperlipidemia
- Cytopenias
- GI toxicity

**PTDM**
Monitor for Drug Interactions (CNI)

- CNIs metabolized - CPY 450 3A4 or gp 170 (MDR1- gene)

- Commonly encountered drugs that interacts with CNI:

  **Increase CNI (Cyclosporine or Tacrolimus) levels:**
  - Azole antifungals: fluconazole, clotrimazole
  - Macrolide antibacterials: erythromycin, clarithromycin
  - Calcium channel blockers: verapamil and Cardizem
  - Protease inhibitors

  **Decreases CNI levels:**
  - Anticonvulsants: phenobarbital, carbamazepine
  - Antitubercular drugs: INH, Rifampicin.

Transplant Outcomes

You can’t possibly account for every possible treatment outcome
In Early 90s – Rejection rates were >50 %
Now – Less than 10 %
Short-term Outcome

- Decrease in acute rejection may be related to the development of newer (improved) immunosuppressive agents and/or regimens.

Incidence of Early Acute Rejection Episodes up to 2 Years Posttransplant

# Renal Transplantation Outcomes

<table>
<thead>
<tr>
<th></th>
<th>1yr</th>
<th>3yrs</th>
<th>5yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Deceased-donor tx</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graft Survival</td>
<td>89.4%</td>
<td>76.3%</td>
<td>64.7%</td>
</tr>
<tr>
<td>Patient Survival</td>
<td>94.8%</td>
<td>88.9%</td>
<td>81.8%</td>
</tr>
<tr>
<td><strong>Living-donor tx</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graft Survival</td>
<td>94.5%</td>
<td>87%</td>
<td>78.4%</td>
</tr>
<tr>
<td>Patient Survival</td>
<td>97.6%</td>
<td>94.6%</td>
<td>91%</td>
</tr>
</tbody>
</table>
Outcomes in Renal Transplantation

- All-cause graft failure
- Return to dialysis or retransplant
- Death with function

Rate/100 pt yrs w/functioning graft

Transplant year
No question about it.
This is a case of rejection.
Goal Post-transplantation

Balancing Immunosuppressive Treatment

Too Much
- Infection
- Malignancy
- CVD
- Nephrotoxic

Too Little
- Allograft Rejection
Major complications Post Transplantation

• **Early complications**
  - Surgical complications
    • Urinary leak
    • Vascular thrombosis
    • Bleeding complications
  - Medical complications
    • Delayed Graft Function – 22%
    • Acute Rejection -10-15%

• **Late Complications**
  - Chronic Allograft Nephropathy
  - Death with Functioning Graft
  - Infections
  - Malignancy
  - Metabolic complications
## Common Causes of Graft Dysfunction

<table>
<thead>
<tr>
<th>Immediate:</th>
<th>Few days – 3 months:</th>
<th>Late (&gt; 3 months):</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. DGF/ATN</td>
<td>1. Volume depletion</td>
<td>1. Rejection</td>
</tr>
<tr>
<td>2. Rejection (Hyperacute or Accelerated)</td>
<td>2. Acute CNI toxicity</td>
<td>2. GN (Rec/ De Novo)</td>
</tr>
<tr>
<td>3. Urinary leak</td>
<td>3. Obstruction/lymphocele</td>
<td>3. CNI toxicity</td>
</tr>
<tr>
<td>5. Vascular occlusion</td>
<td>5. TMA</td>
<td>5. Viral Infections</td>
</tr>
<tr>
<td>6. Athero-embolism</td>
<td>6. Infections (e.g.: BKV)</td>
<td>6. RAS</td>
</tr>
<tr>
<td></td>
<td>7. Recurrent GN</td>
<td>7. CAN</td>
</tr>
</tbody>
</table>

DGF: Delayed Graft Function, TMA: Thrombotic Microangiopathy
GN: Glomerulonephritis, RAS: Renal artery Stenosis, CAN: Chronic allograft nephropathy
Acute cellular rejection

T cell mediated rejection

Incidence <15% in the first year, Early diagnosis is Absolutely Essential
Banff I: Tubulointerstitial – Steroids
Banff II. Endothelialitis – Thymoglobulin
Banff III. Vasculitis – Fibrinoid necrosis ATG & revise immunosuppression
**Acute Humoral rejection**

A: Fibrinoid necrosis  
B: Neutrophils margination PTC  
C: Diffuse strongly positive C4d

**Diagnostic Criteria for Acute humoral Rejection**

1. Allograft Dysfunction with Evidence of Tissue injury
2. C4d Immunostain Positive
3. Donor Specific Antibody Positive
Treatment of Rejection

- **Acute Cellular Rejection**
  - Corticosteroids (Grade I)
  - Anti-thymocyte globulin (Grade > II)

- **Acute Humoral Rejection**
  - Intravenous Immunoglobulin (IVIG)
  - Rituximab
  - Plasmapheresis

Site of action, adverse effects and Drug interactions
Major Causes of Death in Kidney Transplantation

Infections: 26.3%
Malignancy: 10.7%
CVD: 43.5%
Other: 19.4%

Adult, first-time, kidney-only transplant recipients, 1995–2003, who died with functioning graft (N=10,648). Cause of death obtained from OPTN when available, otherwise taken from the ESRD Death Notification form.

2006 ADR
Mortality after Renal Transplantation

- CVD: 38%
- Infection: 29%
- Malignancy: 12%
- Others: 10.50%
- Unknown: 10.50%

N=1200, 1995-2004
Infectious causes for mortality
Post-Transplantation

Polyoma Virus Nephropathy


- First reported in 1995 and associated with polyomavirus type BK. JC virus (PMLE) and SV 40 in same family
- 90% seroprevalence rate worldwide
- Mainly the disease of kidney tx patients. Association with anti-rejection treatment and the degree of immunosuppression
Post-Transplant Malignancies

Cincinnati Transplant Tumor Registry

- Skin + Lip
- Lymphoma
- Lung
- Uterus
- Kaposi
- Colon/Rectum
- Kidney
- Breast
- Head + Neck
- Perineum
- Other

Lymphoma: 37%
Skin and Lip: 17%
6 - 3%
Recipient of organ transplants are at higher risk for malignancy

- Related to impaired immune surveillance as a result of immunosuppression.
- Skin cancer most common: sun protection.
- Routine cancer screening.

Specific malignancies:
- Kaposi sarcoma – HHV 8
- Post-transplant lymphoproliferative disorder (PTLD) - EBV
Individualizing Immunosuppression Therapy

- **Overall immunosuppression goals**
  - Improve short- and long-term survival
  - Maximize efficacy, minimize toxicity and posttransplant complications

- **High immunologic risk**
  - Highly sensitized
  - Nonprimary transplant
  - African American ethnicity
  - Deceased donor source
  - Poor HLA match

- **Low immunologic risk**
  - Nonsensitized
  - Asian ethnicity
  - Elderly
  - Living donor source
  - Good HLA match

---

Barriers /Solutions for Transplantation

1. Organ Shortage Barrier : Demand –supply Crisis
2. Immunological barrier: Highly Sensitized status
3. Socio-Economic Barrier
4. Co-morbidity Barriers
Demand-Supply Crisis

Waitlist and Transplant Activity for Kidneys, 2000-2009

- Waiting List at Year End
- Total Kidney Transplants
- Deaths on Waiting List

Kidney Waiting list candidates > 90,000

Source: OPTN/SRTR Annual Report Tables 1.3, 1.6, 1.7
Impact of Demand-Supply Crisis

Number on the wait list is >90,000
Time on the wait list is increasing >5 yrs
Longer the waiting time, poorer the outcome
Mortality on the waitlist is increasing
Increase in Deceased Donor Renal Transplantation

- SCD: Standard Criteria Donor - 76%
- ECD: Extended Criteria Donor - 7%
- DCD: Donation After Cardiac Death - 16%

Line graph showing the increase in the number of transplants from 1997 to 2006:
- SCD: Increase by 15%
- ECD (includes DCD/ECD): Increase by 50%
- DCD: Increase by 726%
Sensitization and Crossmatch (CXM)

- ABO compatibility & Negative CXM - is Essential (Not absolute)
- Sensitization:
  - Presence of cytotoxic Abs against donor HLA class I or II Ag (PRA- CDC or FLOW cytometry)
- High risk for sensitization
  - Multiparous, previous transplant, blood transfusions
- 30% on the Waiting List are sensitized (>20% PRA)
  - Waiting time is at least twice longer
- Positive XM (Cytotoxic Abs) virtually excludes Tx.
  - 80 – 90 % experience hyperacute or accelerated antibody rejection
Desensitization Protocol

Higher cumulative immunosuppression
Resource consuming – Manpower and money
Paired Kidney Donation

The evolution of paired exchange:

- Organ allocation cost is an increasingly large component of overall cost

- Paired kidney donation

Traditional Paired Exchange

Two Pair Exchange

Three Pair Exchange

Chains

Cluster #1

Cluster #2

Cluster #3

Non-directed altruistic donor

Etc.
Future : Tolerance

Immune regulation for reproduction

- Immune suppression (vs. Activation)
- Immune cell apoptosis
- Generation of Tregs (vs. Effector cells)
- Decreased production of inflammatory cytokines
- Hypo-responsiveness of immune cells to antigens or activation signals

Allogeneic antigen priming under the influence of placental factors:
- Estrogen
- Progesterone
- Prostaglandin E2
- Human placental protein 14
- Insulin-like growth factor
- Somatostatin
- Activin-A
- Others

Allogeneic antigen priming under the influence of fetal factors:
- α-fetoalcohol
- Others

Placenta

Maternal circulation

Fetal circulation through the cord

X
Thank You