Chronic Kidney Disease (CKD) Stages

- **Stage 1**
  - GFR > 90 (evidence of renal disease)
- **Stage 2**
  - GFR 60-89
- **Stage 3**
  - GFR 30-59
- **Stage 4**
  - GFR 15-29
- **Stage 5**
  - GFR <15 (including ESRD)

Treatment Options

- Anti-Hypertensives
- Diuretics
- Diabetic control
- Phosphate binders, Calcium, Vitamin D3
- Erythropoietin, Iron
- Sodium Bicarbonate
- A.C.E. Inhibitor, All Receptor Blocker
- Dietary restrictions
  - Potassium, Sodium, Water, Protein,

END-STAGE RENAL DISEASE

Definition

- Irreversible reduction in intrinsic renal function that which can be compensated for by any adjustments in diet or medications, such that there is continuing accumulation of nitrogenous waste products, sodium, potassium, water, and/or acid, ...leading to intractable clinical illness (uremia).

Causes of End-Stage Renal Disease

- Diabetes > 40%
- Hypertension 27.2%
- Glomerulonephritis 12.4%
- Cystic Diseases 2.9%
- Interstitial Nephritis 2.6%
- Collagen Vascular Diseases 2.1%
- Obstructive Uropathy 1.9%

USRDS, 2001

ESRD Prevalent counts & adjusted rates by primary diagnosis

Figure 2.30

(December 31 point prevalent ESRD patients; rates adjusted for age, gender, & race.)

USRDS 2007 Annual Data Report

Incident counts & adjusted rates, by primary diagnosis

Incident ESRD patients; rates adjusted for age, gender, & race.

USRDS Annual Data Report 2007
**Indications for Renal Replacement Therapy**

- Intractable volume overload
- Hyperkalemia
- Anorexia, Nausea, Vomiting, Gastritis
- Lethargy, Seizures, Coma
- Pericarditis
- Bleeding due to platelet dysfunction

**End-Stage Renal Disease**

**Treatment Options**

- Dialysis
  - Hemodialysis
  - Peritoneal Dialysis
- Renal Transplantation
  - Deceased Donor
  - Living Donor

**Projected growth of prevalent ESRD populations, by modality (Markov model)**

- **CONVECTION**
  - Movement of solutes across a semi-permeable membrane carried in the bulk movement of water (hydrostatic pressure, “ultrafiltration”)

- **DIFFUSION**
  - Movement of solutes across a semi-permeable membrane down their concentration gradient

**Dialysis Basic Principles**
Tissue-Blood Equilibration

Peritoneal Dialysis

Peritoneal Membrane

Tissue-Blood Equilibration
**Hemodialysis vs Peritoneal Dialysis**

- Rapid correction of metabolic, fluid imbalance
  - Blood flow 400 ml/min
  - Dialysate flow 500 ml/min
- Cardiovascular instability
- Angio-access required
- Three times weekly
- Better clearance of small molecules

- Gradual correction of metabolic, fluid imbalance
  - Dialysate 2L/6 hours
  - Blood flow ??
- Respiratory embarrassment
- Peritoneal access
- Daily treatments
- Loss of albumin
- Better clearance of "middle molecules"

**Factors determining the clearance of substances by dialysis**

- Molecular size
- Protein binding
- Relative concentration (tissue vs blood vs dialysate)
- Membrane characteristics ("pore size")
- Blood flow ($Q_B$)
- Dialysate flow ($Q_D$)

---

**Relative Concentrations**

<table>
<thead>
<tr>
<th>Blood Solution</th>
<th>Dialysate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>&lt; Dextrose</td>
</tr>
<tr>
<td>Na+</td>
<td>= Na+</td>
</tr>
<tr>
<td>K+</td>
<td>&gt; K+</td>
</tr>
<tr>
<td>HCO₃⁻</td>
<td>&lt; HCO₃⁻</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>&lt; Ca²⁺</td>
</tr>
<tr>
<td>Phos</td>
<td>&gt;&gt;&gt; Ø</td>
</tr>
<tr>
<td>Urea</td>
<td>&gt;&gt;&gt; Ø</td>
</tr>
<tr>
<td>Creatinine</td>
<td>&gt;&gt;&gt; Ø</td>
</tr>
</tbody>
</table>

---

**Hemodialysis: Solute Clearance**

Effect of blood flow and solute size

---

**Peritoneal Dialysis**

Effect on Ultrafiltration of changes in dialysate volume, dwell time, and [glucose]
End-Stage Renal Disease

Treatment Options

- Dialysis
  - Hemodialysis
  - Peritoneal Dialysis
- Renal Transplantation
  - Deceased Donor
  - Living Donor

Renal Transplantation

- Single kidney from the donor implanted into the iliac fossa of the recipient.
- Renal artery and vein are anastomosed to the (external) iliac artery and vein, respectively. The ureter is implanted into the bladder.
- The recipients native kidneys are not removed.
- Major barrier to success is immunologic.

Renal Transplantation (2)

- Advantages (vs Dialysis)
  - Better renal function (gfr 40-80 ml/min)
  - No further need for dialysis
  - Complete correction of fluid and electrolyte abnormalities
  - Improved quality of life
  - Improved longevity (for comparable patients)
- Disadvantages
  - “Lifelong” immunosuppression
  - Possible rejection (likely eventual allograft failure)

USA - 2006

- 18,000 total kidney transplants
  - 55% Deceased Donor
  - 45% Living Donor
  - Living Related Donors
  - Living Un-related donors (spouses, friends)
- Waiting List
  - 75,000

“High Intensity” Hemodialysis (Improved Outcomes in Hemodialysis)

Variables

- Increased duration
  - Same frequency, longer treatments
    - 1 x/week x 6-8 hours
- Increased frequency
  - Daily short treatments
    - 6-7 x/week x 2-2.5 hours
- Increased frequency and duration
  - Daily (Nocturnal), longer treatments
    - 6-7 nights/week x 8 hours
Renal Transplantation
Columbia University Medical Center
2007

- 260 Transplants
  - 142 (55%) Deceased Donor
  - 118 (45%) Living Donor
    - 65% Living Related donor
    - 35% Living-Unrelated Donor (Spousal, Friends)

Allo-immunity
The main barrier to success

- Major Histocompatibility Complex (MHC) encoded proteins
- HLA antigens
  - Class I (HLA A,B - all nucleated cells)
  - Class II (HLA DR - APC’s, B cells, endothelial cells, renal tubular epithelial cells)

Types of Immunosuppressive Medications Used in Renal Transplantation

- Corticosteroids
  - Prednisone, Methylprednisolone
- Lymphocyte Proliferation/Purine Synthesis Inhibitors
  - Mycophenolic acid, Azathioprine
- Calcineurin Inhibitors
  - Cyclosporine, Tacrolimus
- mTOR Inhibitors
  - Sirolimus (Rapamycin)
- Anti-Lymphocyte Antibodies
  - Polyclonal
  - Monoclonal

Sites of Action of Immunosuppressive Medications

Maintenance Immunosuppressive Regimens

Dual/Triple Therapy
Cyclosporine/ + Mycophenolate + Prednisone Tacrolimus

Cyclosporine/ + Sirolimus + Tacrolimus

Sirolimus + Mycophenolate + Prednisone
Current Renal Transplant Survival Rates

<table>
<thead>
<tr>
<th>Time</th>
<th>Deceased donor</th>
<th>Living Donor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 yr</td>
<td>89%</td>
<td>95%</td>
</tr>
<tr>
<td>5 yr</td>
<td>66%</td>
<td>79%</td>
</tr>
<tr>
<td>10 yr</td>
<td>50%</td>
<td>65%</td>
</tr>
</tbody>
</table>

- **Deceased donor**
  - 89% at 1 yr
  - 66% at 5 yr
  - 50% at 10 yr

- **Living Donor**
  - 95% at 1 yr
  - 79% at 5 yr
  - 65% at 10 yr

SRTR 2005 data

Kidney Graft Survival Rates

Living Donor Graft Survival According to Donor Relationship (1988-2000)

Donor Relationship

- HLA-Id: 5,676 22.2%
- Parent: 8,448 12.3%
- Mm Sib: 11,162 14.0%
- Other: 2,831 14.0%
- Spouse: 3,057 14.5%
- Offspring: 5,610 12.5%

Effect of HLA Mismatches on Graft Survival

Renal Transplantation
Matching Donor and Recipient

- **“Essential”**
  - ABO Compatibility
  - Negative cross-match
    - Antibodies reactive with Donor HLA:
      (Donor lymphocytes + Recipient serum + Complement --> Cytolytic antibodies)

- **Desirable**
  - HLA Compatibility
Survival in ESRD: Dialysis vs. Transplant

Five-year survival rate
Dialysis vs. Kidney Transplantation

Challenges to Long-Term Success of Renal Transplantation
- Donor Shortage
- Chronic Allograft Nephropathy (40-50%)
  - Long-term progressive deterioration in renal function
- Patient death with Functioning Allograft (40-50%)
  - Cardiovascular disease
  - Complications of Long-term Immunosuppression

Time on Dialysis vs Transplant Outcome

“Chronic Allograft Nephropathy”
Why do transplants fail?

Pre-transplant
- HLA mismatch
- Acute rejection episodes
- Prior sensitization (PRA, DSA)
- Inadequate immunosuppression

Post-transplant
- Donor Organ Quality
- HLA mismatch
- Acute rejection episodes
- Prior sensitization (PRA, DSA)
- Inadequate immunosuppression
## Future Perspectives in Renal Replacement Therapy

<table>
<thead>
<tr>
<th>Dialysis</th>
<th>Renal Transplantation</th>
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</thead>
<tbody>
<tr>
<td>• Improved (more biocompatible) membranes</td>
<td></td>
</tr>
<tr>
<td>• Improved measures of dialysis adequacy</td>
<td></td>
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<tr>
<td>• Alternative dialysis schedules</td>
<td></td>
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<tr>
<td>• Portable dialysis</td>
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<tr>
<td>• &quot;Artificial kidney&quot;</td>
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<tr>
<td>• New/Improved Immunosuppressive Agents</td>
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<tr>
<td>• Molecular Diagnosis of Rejection</td>
<td></td>
</tr>
<tr>
<td>• Improved Organ Donation Rates</td>
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<tr>
<td>• Xeno-transplantation</td>
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</tr>
<tr>
<td>• Tissue/Organ Culture</td>
<td></td>
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<td>• Tolerance Induction</td>
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