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)

CHRONIC KIDNEY DISEASE Treatment Options

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

Causes of End-Stage Renal Disease

- Diabetes > 40%
- Hypertension 27.2%
- Glomerulonephritis 12.4%
- Cystic Diseases 2.9%
- Interstitial Nephritis 2.8%
- Collagen Vascular Diseases 2.1%
- Obstructive Uropathy 1.9%

END-STAGE RENAL DISEASE Definition

- Irreversible reduction in intrinsic renal function below 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).
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
("Renal Replacement Therapy")

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

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

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of Patients</th>
</tr>
</thead>
</table>
| 2000 | 120
| 2005 | 300
| 2010 | 700
| 2015 | 1,200
| 2020 | 2,000

Counts projected using a Markov model. Original projection uses data through 2000; new projection uses data through 2005.

Dialysis

Basic Principles

- 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 Membrane

SOLUTES, WATER

Blood

Dialysis Fluid

Hollow-Fiber Artificial Kidney

Dialysate Out

Dialysate In

Blood In

Blood Out

USRDS 2007 Annual Data Report
Tissue-Blood Equilibration

Peritoneal Dialysis

Peritoneal Membrane
**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</th>
<th>Dialysate Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>Dextrose</td>
</tr>
<tr>
<td>Na⁺</td>
<td>Na⁺</td>
</tr>
<tr>
<td>K⁺</td>
<td>K⁺</td>
</tr>
<tr>
<td>HCO₃⁻</td>
<td>HCO₃⁻</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>Ca²⁺</td>
</tr>
<tr>
<td>Phos</td>
<td>Ø</td>
</tr>
<tr>
<td>Urea</td>
<td>Ø</td>
</tr>
<tr>
<td>Creatinine</td>
<td>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]
Risk of first all-cause hospitalization, by URR
fig 5.26, incident hemodialysis patients, 1998, adjusted for age, gender, comorbidity, disease severity, & hct, stratified on diabetic status

USRDS, 2001

“High Intensity” Hemodialysis (Improved Outcomes in Hemodialysis)

**Variables**

- **Increased duration**
  - Same frequency, longer treatments
  - 3 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

- Single kidney from the donor implanted into the iliac fossa of the recipient.
- Renal artery and vein are anastamosed 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)

End-Stage Renal Disease

**Treatment Options** (Renal Replacement Therapy)

- **Dialysis**
  - Hemodialysis
  - Peritoneal Dialysis

- **Renal Transplantation**
  - Deceased Donor
  - Living Donor

Renal Transplantation 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
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, Methyl-Prednisolone
• 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

Allo-Immune Activation

Maintenance Immunosuppressive Regimens

Dual/Triple Therapy
Cyclosporine/ + Mycophenolate ± Prednisone Tacrolimus
Cyclosporine/ + Sirolimus ± Prednisone Tacrolimus
Sirolimus + Mycophenolate ± Prednisone
### Current Renal Transplant Survival Rates

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

SRTR 2005 data

### Kidney Graft Survival Rates

- Deceased donor: 89% (66%) 50%
- Living donor: 95% (79%) 65%

SRTR 2005 data

### Effect of HLA Mismatches on Graft Survival

![Graph showing graft survival rates over years posttransplant](image)

Cecka, Clinical Transplants 2000 (p. 12)

### 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

Wolfe, et al NEJM, 1999

Five-year survival rate
Dialysis vs. Kidney Transplantation

In incident dialysis patients & patients receiving a first transplant in the incident year, adjusted for age, gender, race, & primary diagnosis. Incident ESRD patients, 1996, used as reference cohort. Modality determined on first ESRD service date; excludes patients transplanted or dying during the first 90 days.

USRDS

Time on Dialysis vs Transplant
Outcome

Meier-Kriesche, et al. KI, 2000

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
    • Malignancy
    • Infection

“Chronic Allograft Nephropathy”
Why do transplants fail?

**Immuneologics**

- HLA mismatch
- Acute rejection episodes
- Prior sensitization (anti-HLA antibodies)
- Inadequate immunosuppression

**Non-immuneologics**

- Donor Organ Quality
  • Number of nephrons
- Kidney Graft Function/Ischemia-Reperfusion Injury
- Nephrotoxicity of immunosuppressive drugs
  • Cyclosporine, Tacrolimus
- Hypertension
- Hyperlipidemia
- Hyperfiltration
  • (Recurrent/ De Novo Disease)
### Future Perspectives in Renal Replacement Therapy

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