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...
**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).

**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*
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%

USRDS, 2001

Incident counts & adjusted rates, by primary diagnosis

Figure 2.11

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
("Renal Replacement Therapy")

- Dialysis
  - Hemodialysis
  - Peritoneal Dialysis
- Renal Transplantation
  - Deceased Donor
  - Living Donor
Projected growth of prevalent ESRD populations, by modality (Markov model)

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

Blood In

Dialysate In

Dialysate Out

Blood Out
Tissue-Blood Equilibration

Blood

Tissue
Peritoneal Dialysis

Peritoneal Membrane
**Hemodialysis vs Peritoneal Dialysis**

- Rapid correction of metabolic, fluid imbalance
  - Blood flow 400ml/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>Ca++</td>
<td>Ca++</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

![Clearance versus blood flow](Fig. 5-5)
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
End-Stage Renal Disease

Treatment Options
(Renal Replacement Therapy)

• 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)

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)
Co-stimulatory molecules, receptors

APC (Self/Allo)

MHC + alloantigen

T cell Antigen receptor

CD3 complex

T cell

calcineurin

IL-2

mTOR

Antigen-specific
Activated
Cytotoxic T cells
Antibody-producing B 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

Maintenance Immunosuppressive Regimens

**Dual/Triple Therapy**

- **Cyclosporine/ Tacrolimus**
  - Mycophenolate  
  - Prednisone

- **Cyclosporine/ Tacrolimus**
  - Sirolimus  
  - Prednisone

- **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

Cecka, Clinical Transplants 2000 (p. 2)
Living Donor Graft Survival According to Donor Relationship (1988-2000)

[Cocka, Clinical Transplants 2001 (p. 4)]

Effect of HLA Mismatches on Graft Survival

[Cocka, 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

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
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

Waitlist and Transplant Activity for Kidneys, 1994-2003

- 2007
  - 75,000 on waitlist
  - 32,000 added to waitlist
  - 18,000 transplants

Source: 2004 OPTN/SRTR Annual Report Tables 1.3, 1.5, 1.7
Time on Dialysis vs Transplant Outcome

“Chronic Allograft Nephropathy”

Why do transplants fail?

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

Non-immunologic
- Donor Organ Quality
  - Number of nephrons
  - Delayed Graft Function/Ischemia-Reperfusion Injury
- Nephrotoxicity of immunosuppressive drugs
  - Cyclosporine, Tacrolimus
- Hypertension
- Hyperlipidemia
- Hyperfiltration
- (Recurrent/De Novo Disease)

Meier-Kreische, et al. KI, 2000
## Future Perspectives in Renal Replacement Therapy

### Dialysis
- Improved (more biocompatible) membranes
- Improved measures of dialysis adequacy
- Alternative dialysis schedules
- Portable dialysis
- “Artificial kidney”

### Renal Transplantation
- New/Improved Immunosuppressive Agents
- Molecular Diagnosis of Rejection
- Improved Organ Donation Rates
- Xeno-transplantation
- Tissue/Organ Culture
- Tolerance Induction