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, All 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).

Causes of End-Stage Renal Disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>&gt; 40%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>27.2%</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>12.4%</td>
</tr>
<tr>
<td>Cystic Diseases</td>
<td>2.9%</td>
</tr>
<tr>
<td>Interstitial Nephritis</td>
<td>2.8%</td>
</tr>
<tr>
<td>Collagen Vascular Diseases</td>
<td>2.1%</td>
</tr>
<tr>
<td>Obstructive Uropathy</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

USRDS, 2001
End-Stage Renal Disease

Treatment Options
(Renal Replacement Therapy)

• Dialysis
  – Hemodialysis
  – Peritoneal Dialysis
• Renal Transplantation
  – Cadaver Donor
  – Living Donor

Indications for Renal Replacement Therapy

• Intractable volume overload
• Hyperkalemia
• Anorexia, Nausea, Vomiting, Gastritis
• Lethargy, Seizures, Coma
• Pericarditis
• Bleeding due to platelet dysfunction
December 31st point prevalent counts, by ESRD Treatment Modality - USRDS 2001

Incident & prevalent ESRD patient counts, by modality
**Number of incident & point prevalent ESRD patients projected to 2010**

![Graph showing the number of patients and projections](image)

**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
Tissue-Blood Equilibration

To dialyzer

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>&lt;</td>
</tr>
<tr>
<td>Na+</td>
<td>=</td>
</tr>
<tr>
<td>K+</td>
<td>&gt;</td>
</tr>
<tr>
<td>HCO3⁻</td>
<td>&lt;</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>&lt;</td>
</tr>
<tr>
<td>Phos</td>
<td>&gt;&gt;&gt;</td>
</tr>
<tr>
<td>Urea</td>
<td>&gt;&gt;&gt;</td>
</tr>
<tr>
<td>Creatinine</td>
<td>&gt;&gt;&gt;</td>
</tr>
</tbody>
</table>

Dextrose
Na⁺
K⁺
HCO₃⁻
Ca²⁺
Ø
Ø
Ø

Hemodialysis: Solute Clearance

Effect of blood flow and solute size

![Graph showing clearance versus blood flow for different substances](image)

Fig. 5-5. Clearance versus blood flow.
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 - 2005**

- 17,000 transplants
  - 55% Deceased Donor
  - 45% Living Donor
    - Living Related Donors
    - Living Un-related donors (spouses, friends)

- **Waiting List**
  - 70,000
**Renal Transplantation**
Columbia University Medical Center

- **199 Transplants 2005**
  - 93 (47%) Deceased Donor
  - 106 (53%) Living Donor
    - 65% Living Related donor
    - 35% Living-Unrelated Donor (Spousal, Friends)

---

**Allograft Immunogenicity**

- 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)
Allo-Immune Activation

Types of Immunosuppressive Medications Used in Renal Transplantation

- **Corticosteroids**
  - Prednisone, Methyl-prednisolone
- **Lymphocyte Proliferation/Purine Synthesis Inhibitors**
  - Mycophenolate mofetil, Azathioprine
- **Calcineurin Inhibitors**
  - Cyclosporine, Tacrolimus
- **mTOR Inhibitors**
  - Sirolimus (rapamycin)
- **Anti-Lymphocyte Antibodies**
  - Polyclonal
  - Monoclonal
Sites of Action of Immunosuppressive Medications

Maintenance Immunosuppressive Regimens

**Triple Therapy**

- Cyclosporine/ + Mycophenolate ± Prednisone
- Tacrolimus

- Cyclosporine/ + Sirolimus ± Prednisone
  Tacrolimus

- Sirolimus + Mycophenolate ± Prednisone
Current Renal Transplant Survival Rates

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

SRTR 2005 data

Kidney Graft Survival Rates

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

Donor | n  | t 1/2
--- | --- | ---
HLA-Id | 5,676 | 22.2
Parent | 8,448 | 12.3
mm Sib | 11,162 | 14.0
Other | 2,531 | 14.0
Spouse | 3,057 | 14.5
Unrel | 2,113 | 13.6
Offspring | 5,610 | 12.5

Effect of HLA Mismatches on Graft Survival

HLA MM | n  | T1/2
--- | --- | ---
0 | 4,566 | 15.5
1-2 | 4,238 | 12.3
3-4 | 10,435 | 13.2
5-6 | 4,584 | 11.0

Cecka, Clinical Transplants 2001 (p.4)

Cecka, Clinical Transplants 2000 (p. 12)
Relative Risk of Graft Failure with One or Two Mismatches at Each HLA Locus as Compared with Zero Mismatches

![Graph showing relative risk with different numbers of mismatches at different HLA loci.]


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

Survival: Transplant vs Dialysis

Relative mortality risks

<table>
<thead>
<tr>
<th>Dialysis - Wait List (WL) vs non-Wait List:</th>
<th>RR</th>
<th>0.43-0.55</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transplant vs WL Dialysis: (1st 2 wks)</td>
<td>RR</td>
<td>2 - 5</td>
</tr>
<tr>
<td>Transplant vs WL Dialysis: (146 -377 d)</td>
<td>RR</td>
<td>1</td>
</tr>
<tr>
<td>Transplant vs WL Dialysis: (long-term)</td>
<td>RR</td>
<td>0.26 - 0.41</td>
</tr>
</tbody>
</table>

Wolfe et al, USRDS Database, 1998 ASN
Challenges to Long-Term Success of Renal Transplantation

- Donor Shortage
- Chronic Allograft Nephropathy
  - Long-term progressive deterioration in renal function
- Patient death
  - Cardiovascular disease
  - Complications of Long-term Immunosuppression
    - Malignancy
    - Infection

Time on Dialysis vs Transplant Outcome

Meier-Kreische, et al. KI, 2000

Kidney Graft Survival Rates

Cecka, Clinical Transplants 2000 (p. 2)
### Chronic Allograft Nephropathy

**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)

### 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