

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...

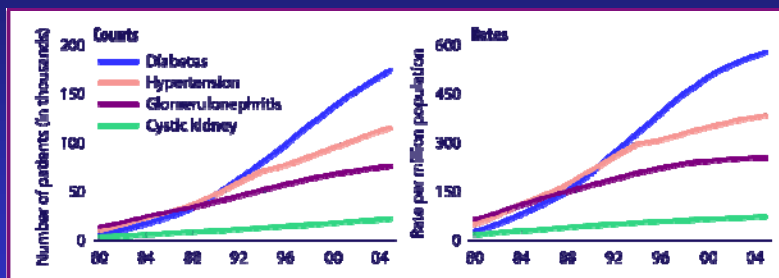
END-STAGE RENAL DISEASE

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

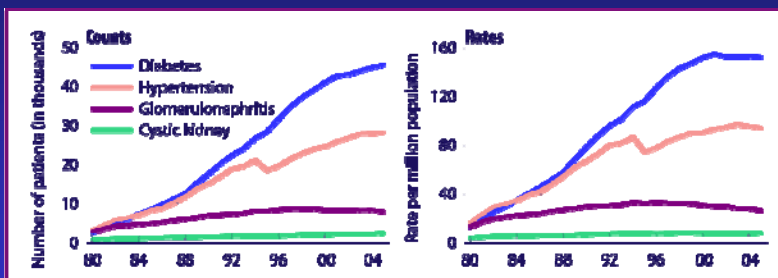
Causes of End-Stage Renal Disease

- 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

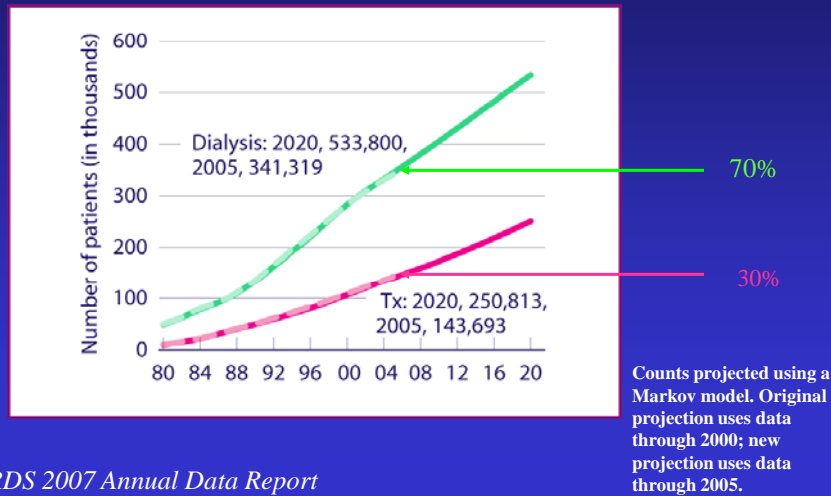
End-Stage Renal Disease

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)

Figure 2.38



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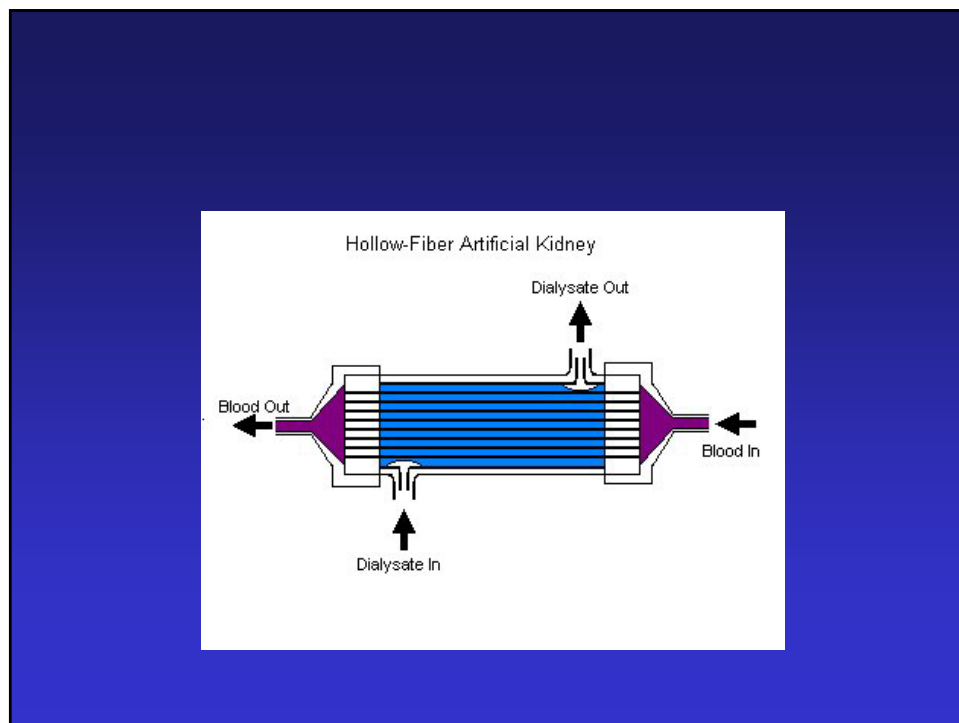
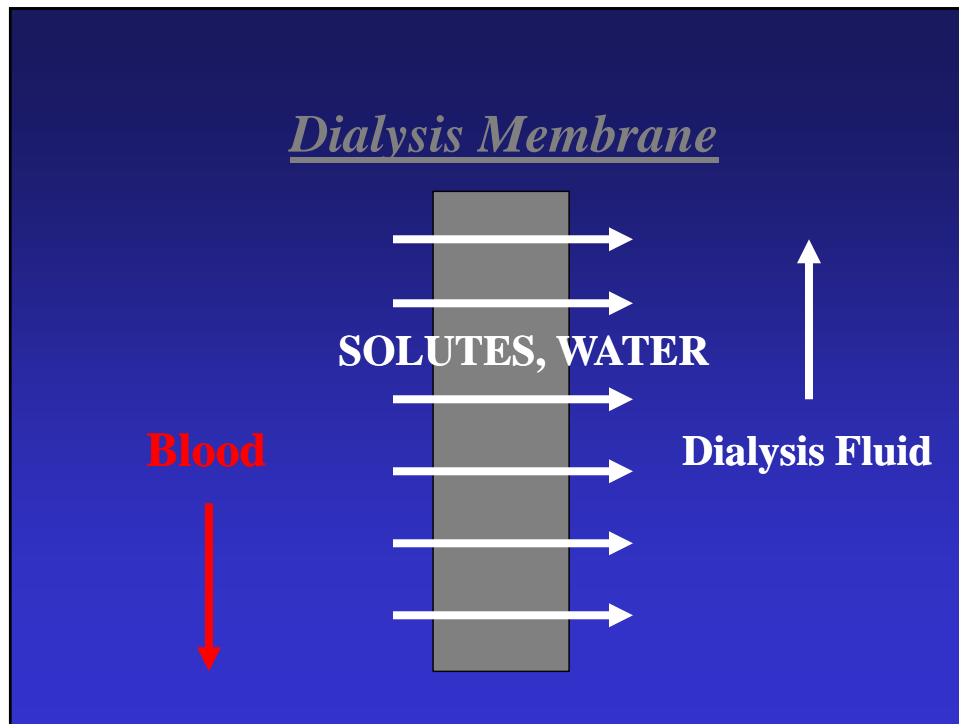
Dialysis Basic Principles

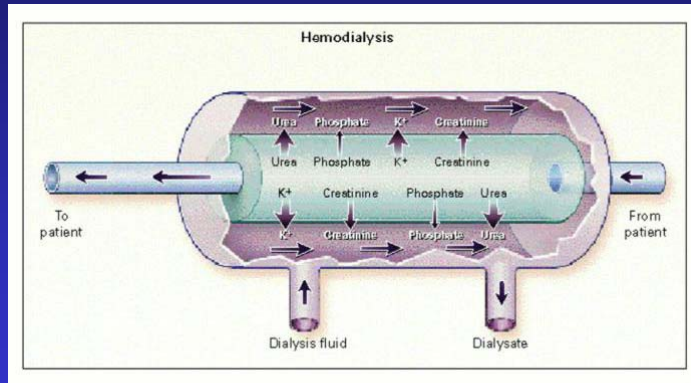
- CONVECTION

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

- DIFFUSION

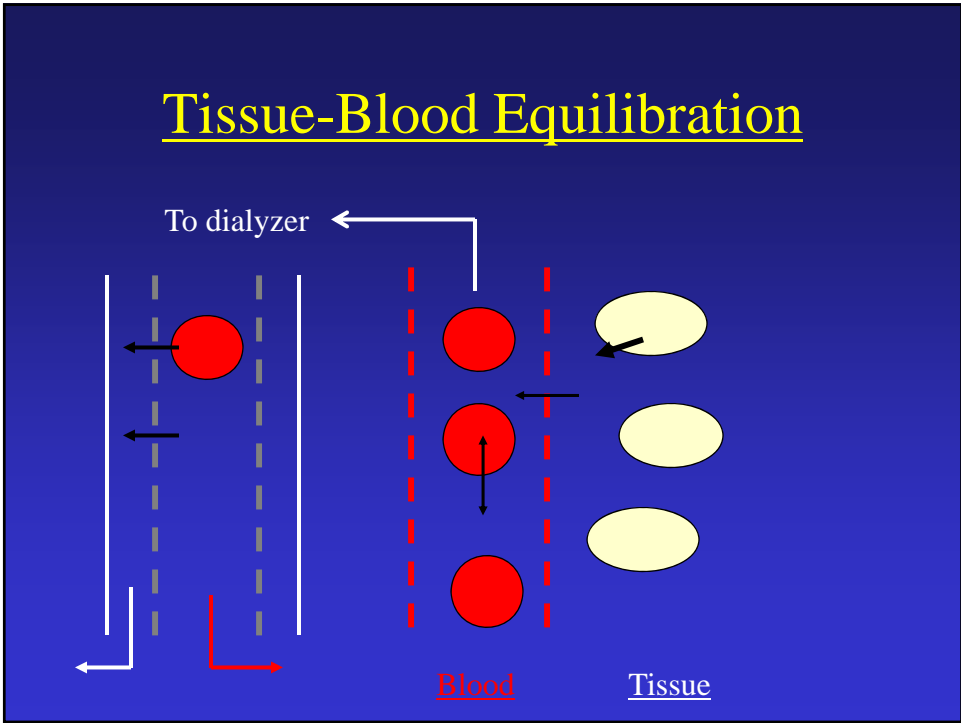
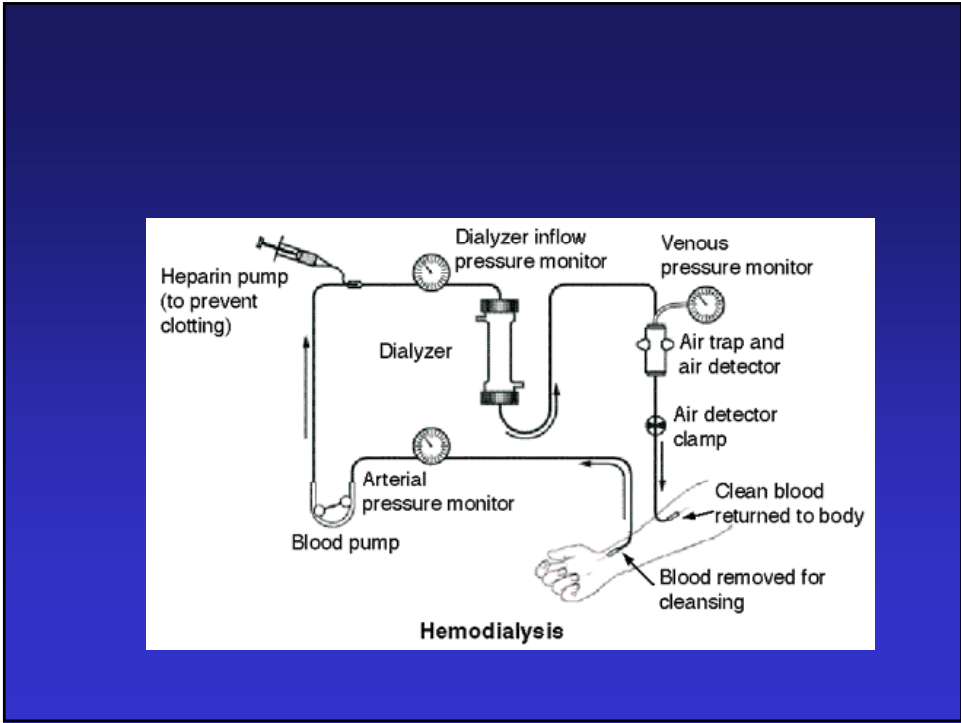
- Movement of solutes across a semi-permeable membrane down their concentration gradient



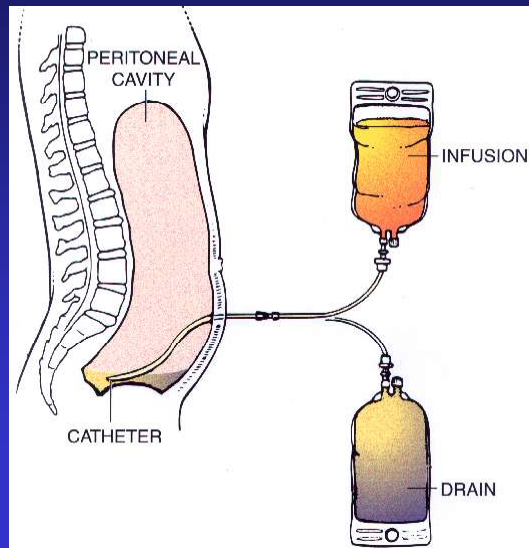


New Eng J Med, 1997

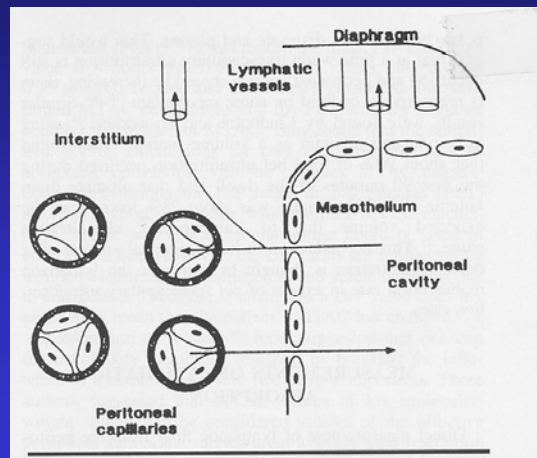




Peritoneal Dialysis



Peritoneal Membrane



Hemodialysis vs Peritoneal Dialysis

- | | |
|---|---|
| <ul style="list-style-type: none"> • Rapid correction of metabolic, fluid imbalance <ul style="list-style-type: none"> – Blood flow 400ml/min – Dialysate flow 500 ml/min • Cardiovascular instability • Angio-access required • Three times weekly • Better clearance of small molecules | <ul style="list-style-type: none"> • Gradual correction of metabolic, fluid imbalance <ul style="list-style-type: none"> – 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

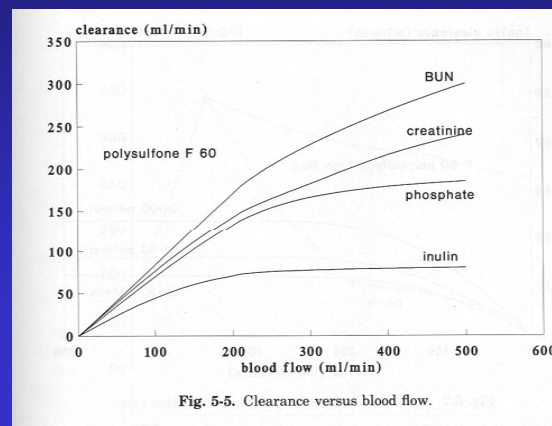
- Molecular size
- Protein binding
- Relative concentration (tissue vs blood vs dialysate)
- Membrane characteristics (“pore size”)
- Blood flow (Q_B)
- Dialysate flow (Q_D)

Relative Concentrations

<u>Blood</u>		<u>Dialysate Solution</u>
Glucose	<	<i>Dextrose</i>
Na ⁺	=	Na ⁺
K ⁺	>	K ⁺
HCO ₃ ⁻	<	<i>HCO₃⁻</i>
Ca ⁺⁺	<	<i>Ca⁺⁺</i>
<i>Phos</i>	>>>	∅
<i>Urea</i>	>>>	∅
<i>Creatinine</i>	>>>	∅

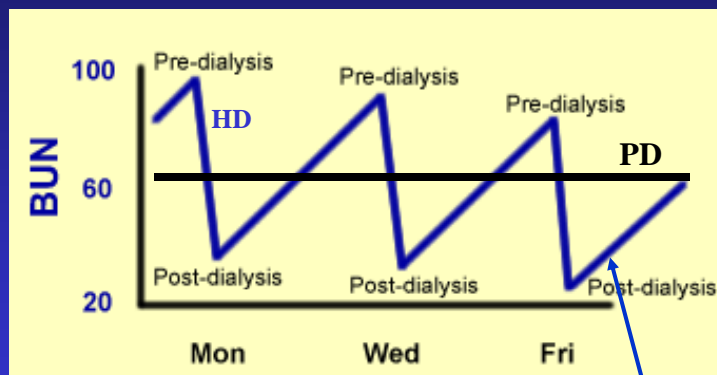
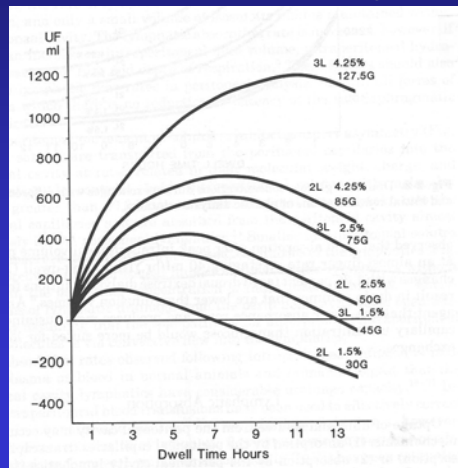
Hemodialysis: Solute Clearance

Effect of blood flow and solute size



Peritoneal Dialysis

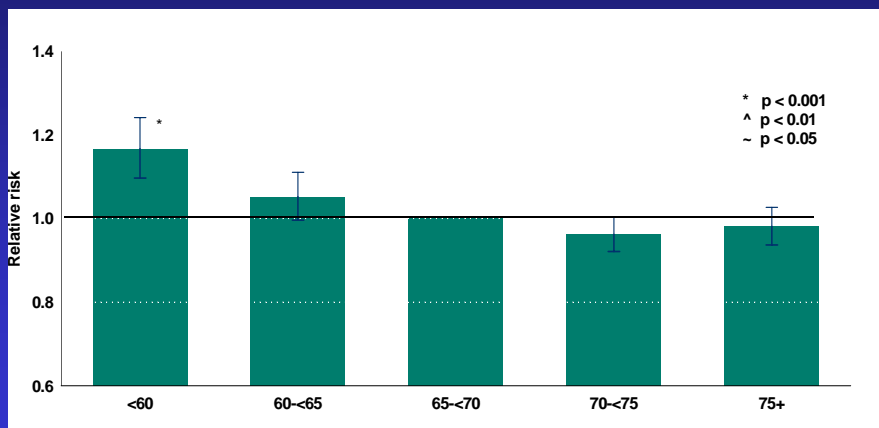
Effect on Ultrafiltration of changes in dialysate volume, dwell time, and [glucose]



HD

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

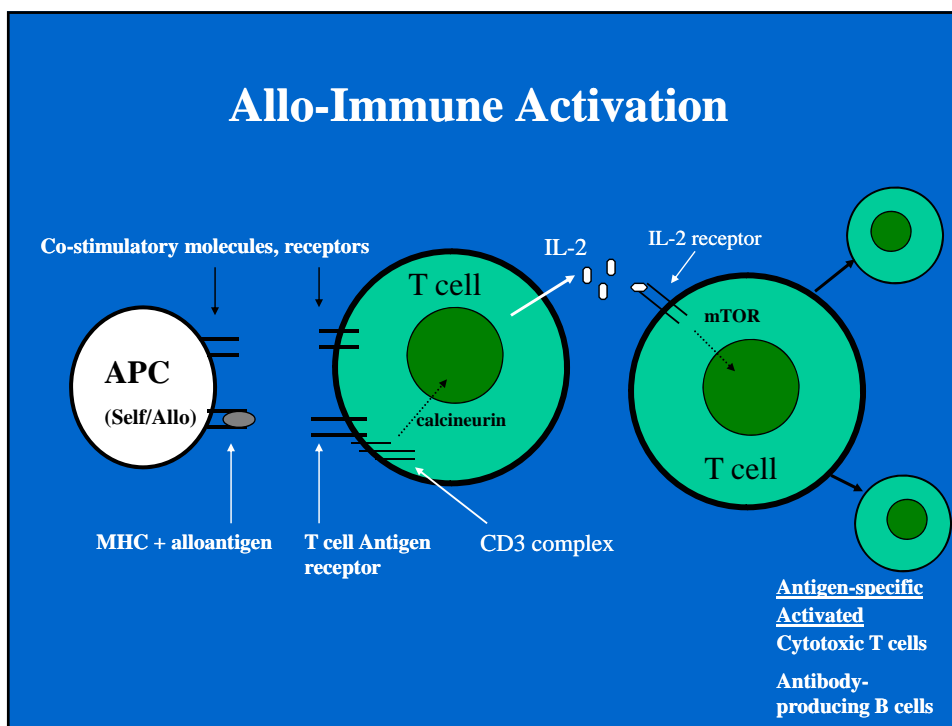
2007

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

Allo-immunity

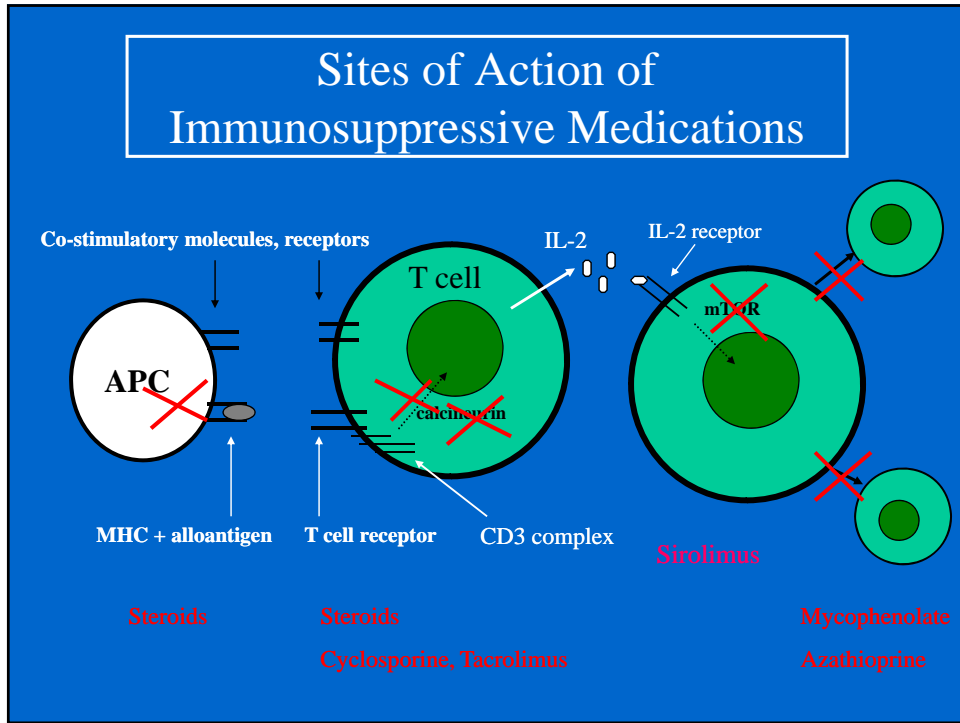
The main barrier to success

- **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)



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



Maintenance Immunosuppressive Regimens

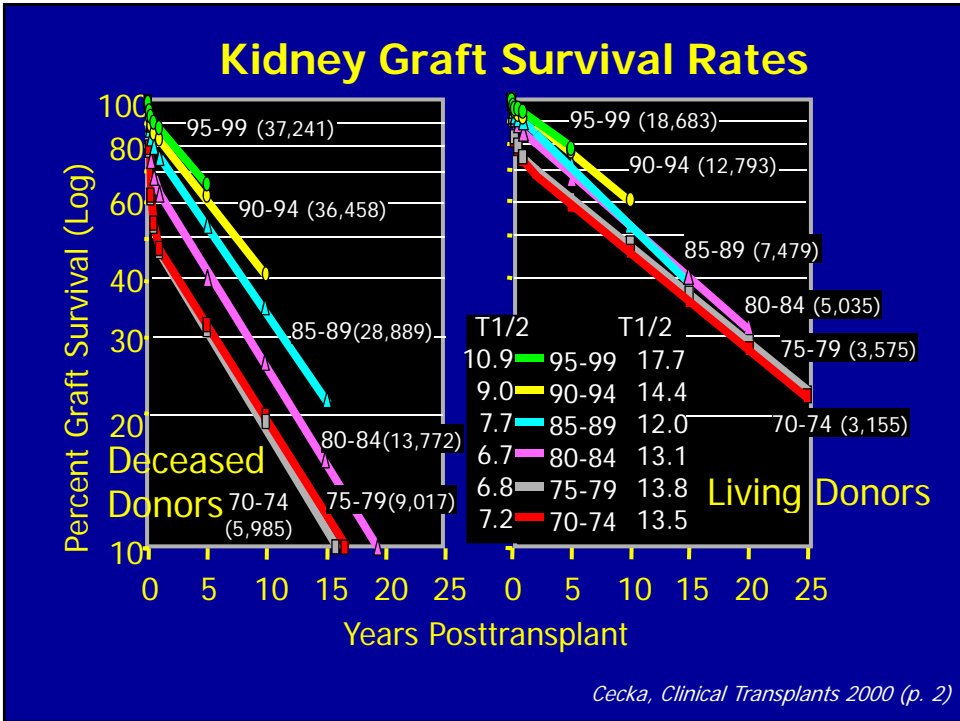
Dual/Triple Therapy

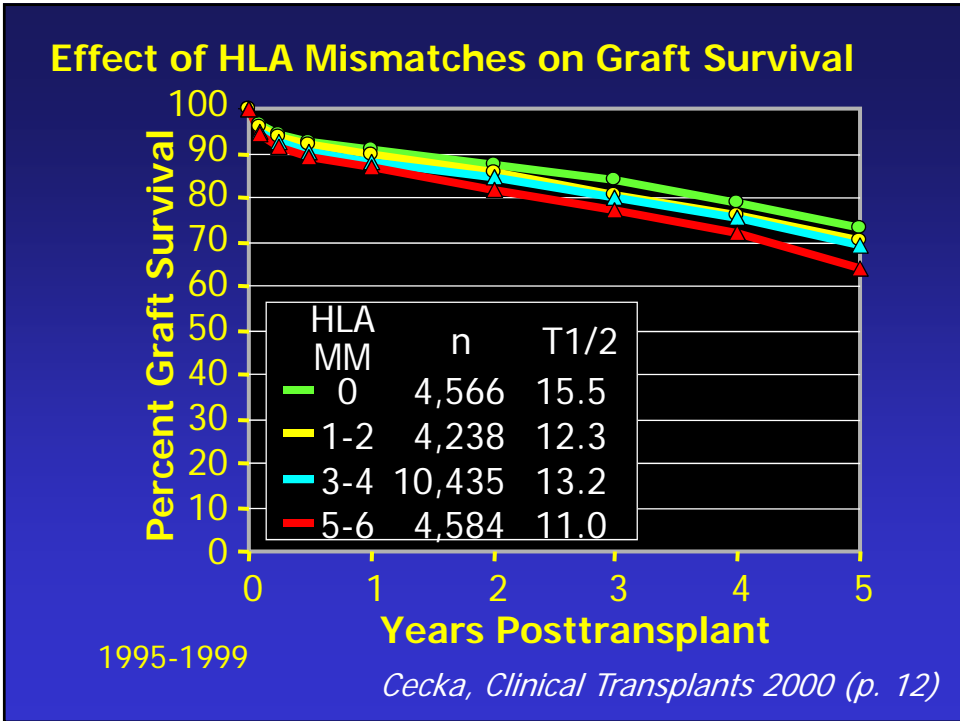
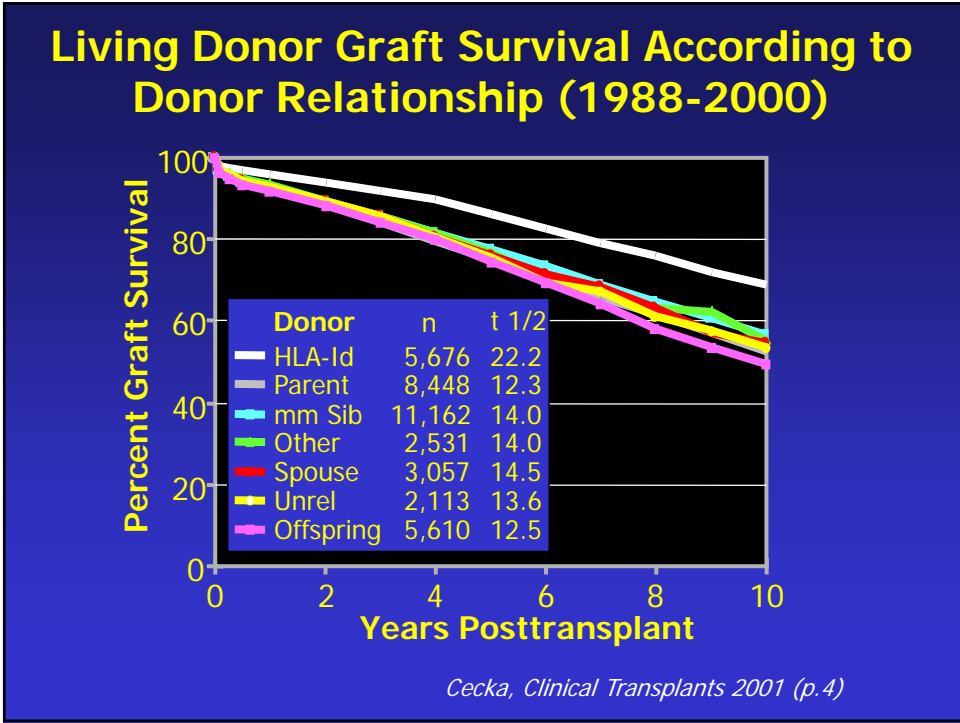
Cyclosporine/ Tacrolimus	+	Mycophenolate	±	Prednisone
Cyclosporine/ Tacrolimus	+	Sirolimus	±	Prednisone
Sirolimus	+	Mycophenolate	±	Prednisone

Current Renal Transplant Survival Rates

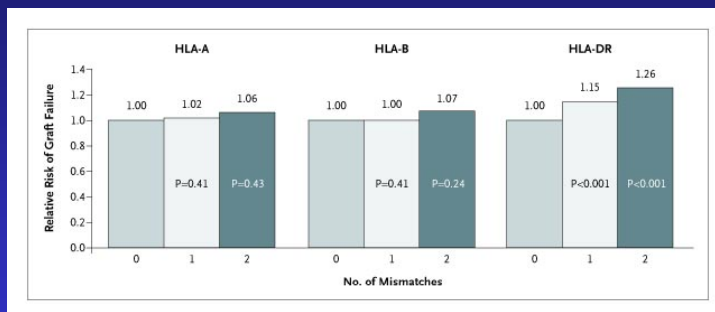
	<u>1 yr</u>	<u>5 yr</u>	<u>10 yr</u>
• Deceased donor	89 %	66%	50%
• Living Donor	95 %	79%	65%

SRTR 2005 data





Relative Risk of Graft Failure with One or Two Mismatches at Each HLA Locus as Compared with Zero Mismatches



Roberts, J. P. et. al. N Engl J Med 2004;350:545-551



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

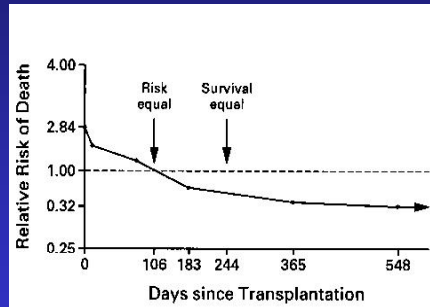
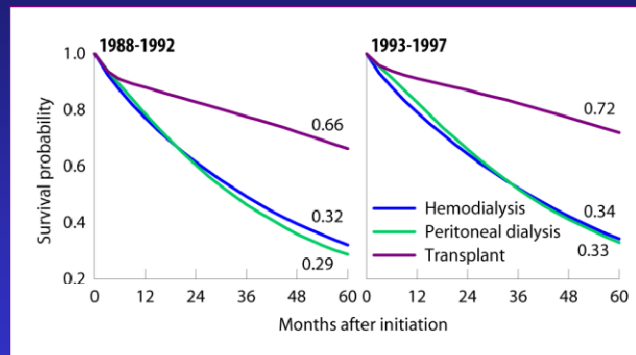


Figure 2. Adjusted Relative Risk of Death among 23,275 Recipients of a First Cadaveric Transplant.

Wolfe, et al *NEJM*, 1999

Five-year survival rate Dialysis vs. Kidney Transplantation



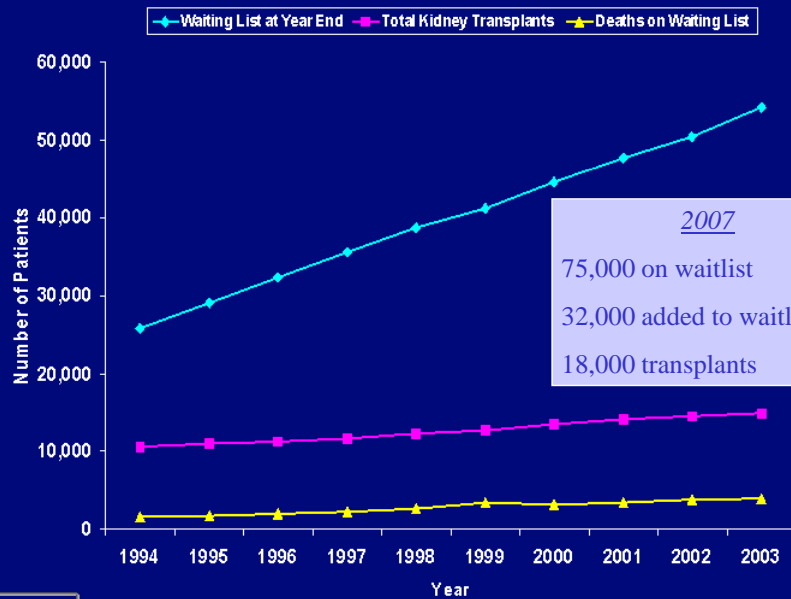
Incident dialysis patients & patients receiving a first transplant in the incident year; adjusted for age, gender, race, & primary diagnosis. Incident ESRD patients, 1996, used as reference cohort. Modality determined on first ESRD service date; excludes patients transplanted or dying during the first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

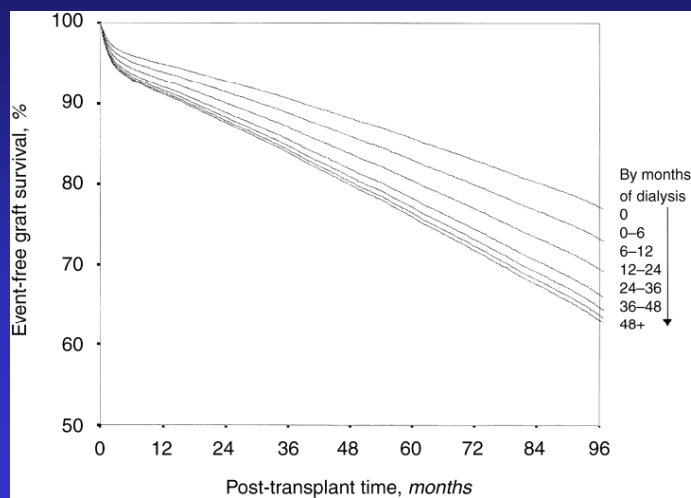


2007
 75,000 on waitlist
 32,000 added to waitlist
 18,000 transplants



Source: 2004 OPTN/SRTR Annual Report Tables 1.3, 1.6, 1.7

Time on Dialysis vs Transplant Outcome



Meier-Kreische, et al. KI, 2000

“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)

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