

## 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).

### 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

# End-Stage Renal Disease

## Treatment Options *(Renal Replacement Therapy)*

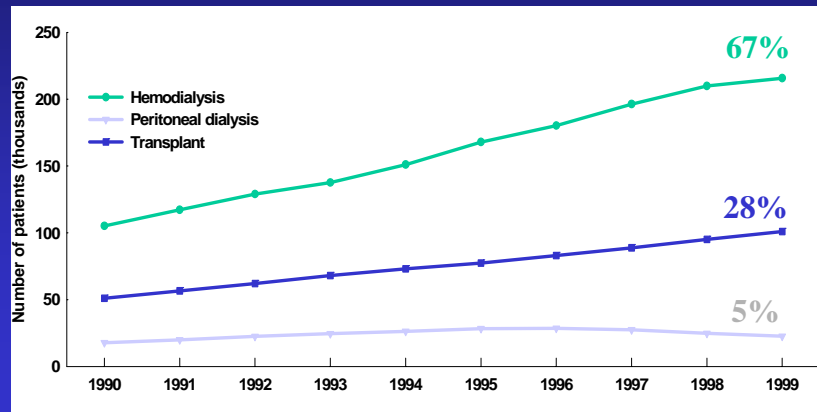
- Dialysis
  - Hemodialysis
  - Peritoneal Dialysis
- Renal Transplantation
  - Cadaver Donor
  - Living Donor

## Indications for Renal Replacement Therapy

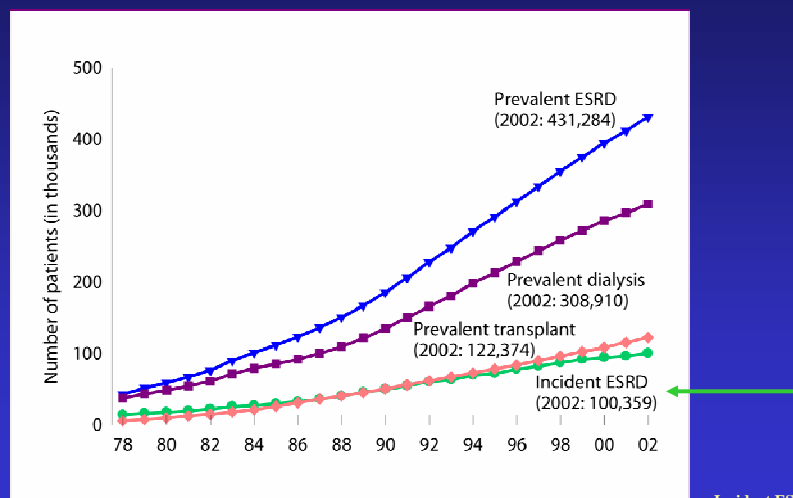
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- Intractable volume overload
- Hyperkalemia
- Anorexia, Nausea, Vomiting, Gastritis
- Lethargy, Seizures, Coma
- Pericarditis
- Bleeding due to platelet dysfunction

## December 31<sup>st</sup> point prevalent counts, by ESRD Treatment Modality - USRDS 2001

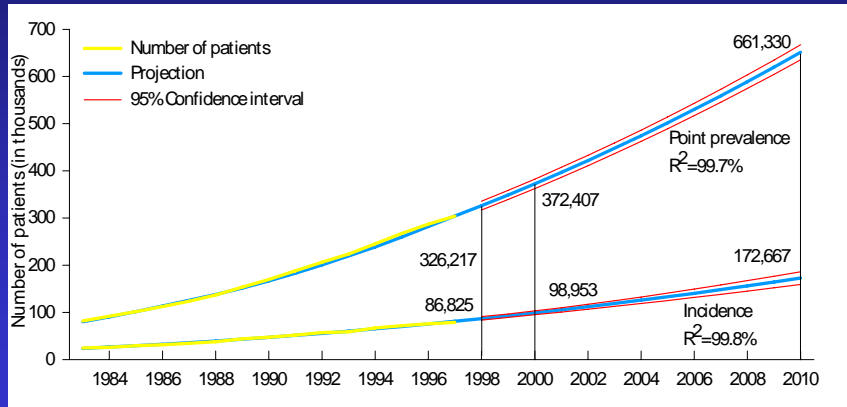


## Incident & prevalent ESRD patient counts, by modality



Incident ESRD patients & December 31 point prevalent patients.

## Number of incident & point prevalent ESRD patients projected to 2010



USRDS 2000

## Dialysis Basic Principles

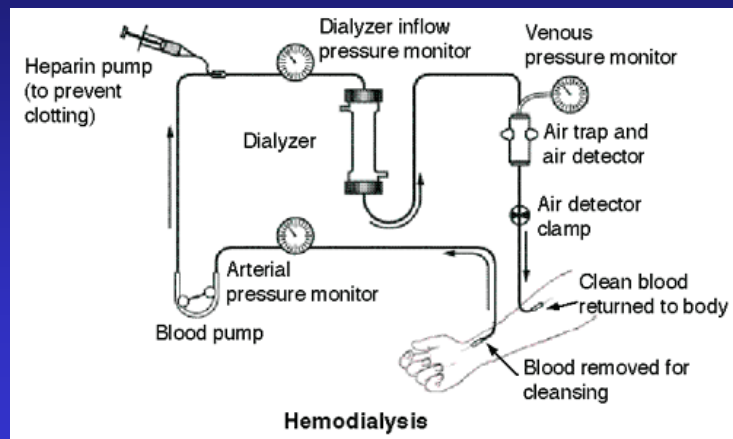
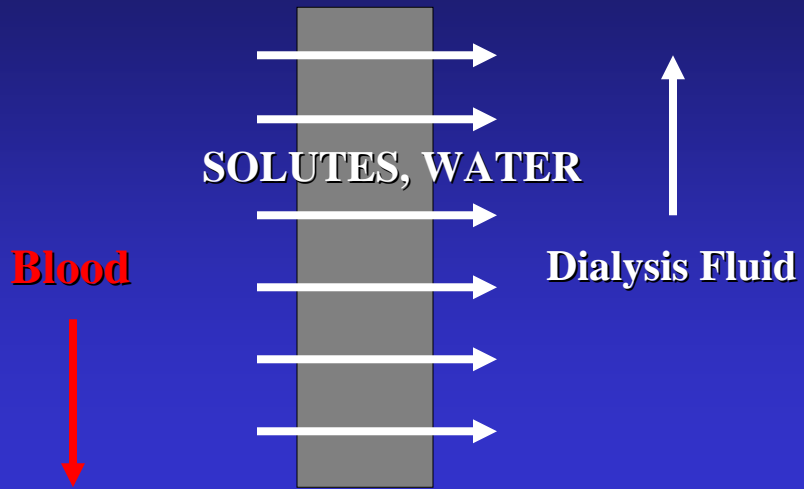
### - CONVECTION

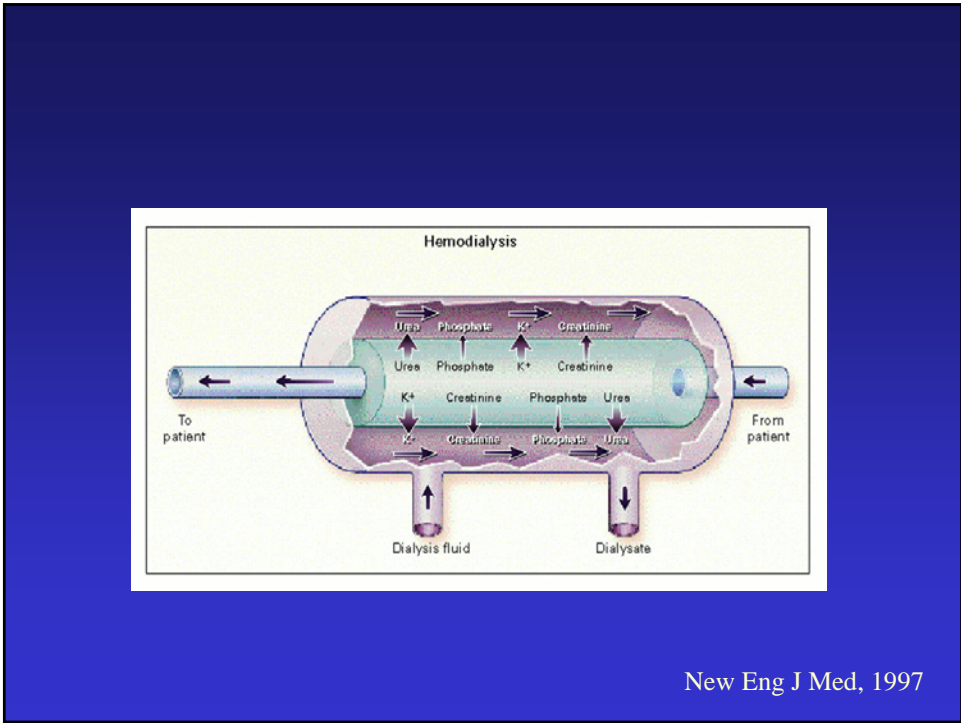
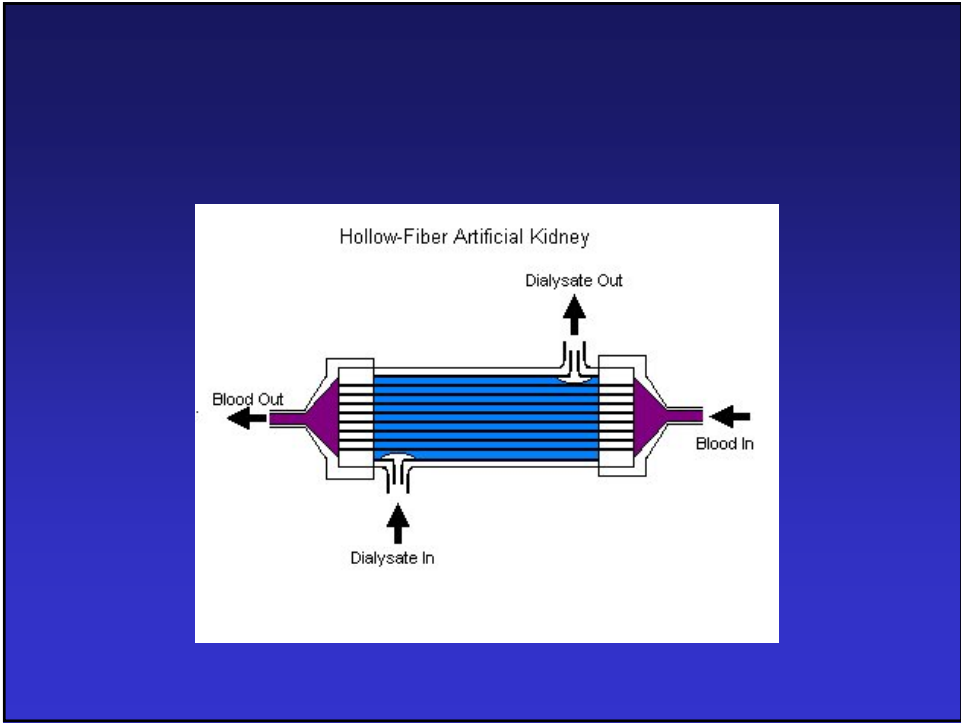
- Movement of solutes across a semi-permeable membrane carried in the bulk movement of water (hydrostatic pressure, “ultrafiltration”)

### - DIFFUSION

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

## Dialysis Membrane

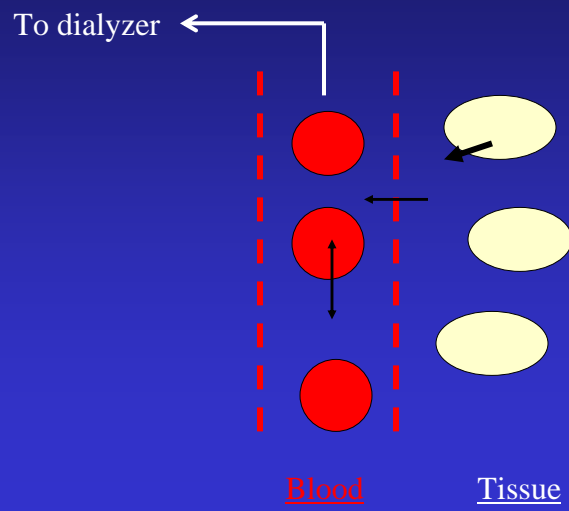




New Eng J Med, 1997

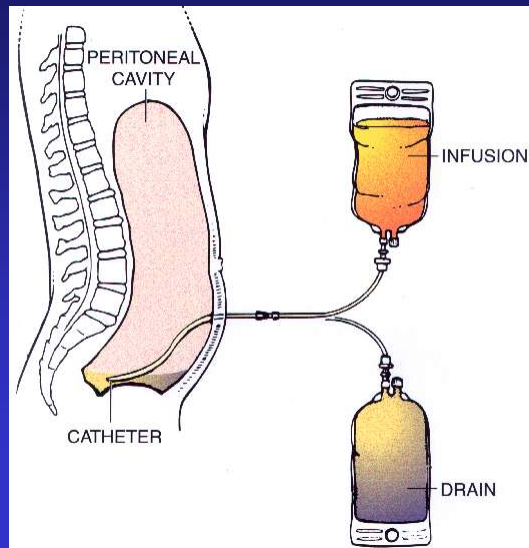


## Tissue-Blood Equilibration

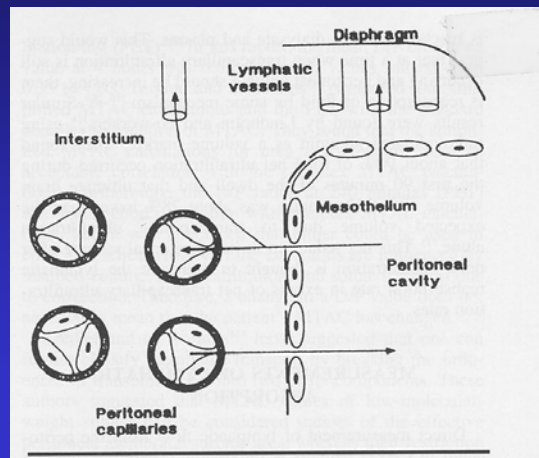




# Peritoneal Dialysis



# 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

<u>Blood</u>		<u>Dialysate Solution</u>
Glucose	<	Dextrose
Na <sup>+</sup>	=	Na <sup>+</sup>
K <sup>+</sup>	>	K <sup>+</sup>
HCO <sub>3</sub> <sup>-</sup>	<	HCO <sub>3</sub> <sup>-</sup>
Ca <sup>++</sup>	<	Ca <sup>++</sup>
Phos	>>>	∅
Urea	>>>	∅
Creatinine	>>>	∅

## Hemodialysis: Solute Clearance

Effect of blood flow and solute size

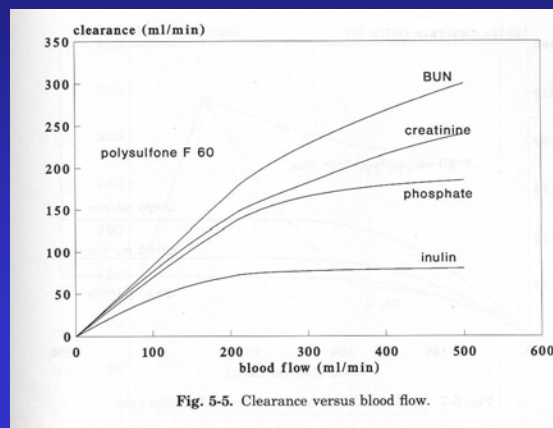
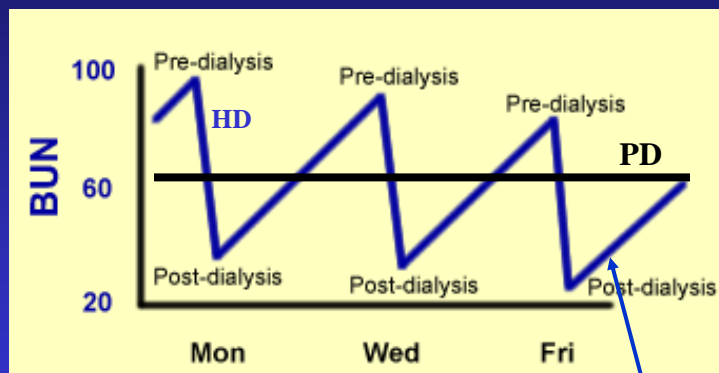
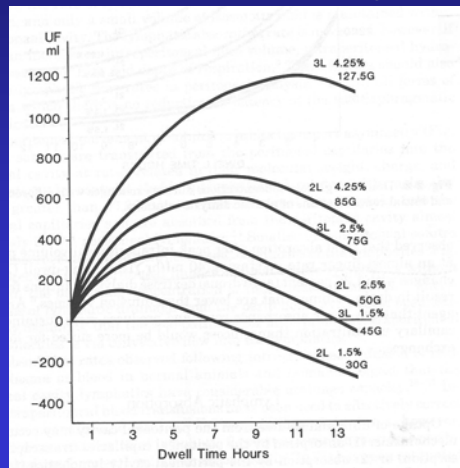


Fig. 5-5. Clearance versus blood flow.

## Peritoneal Dialysis

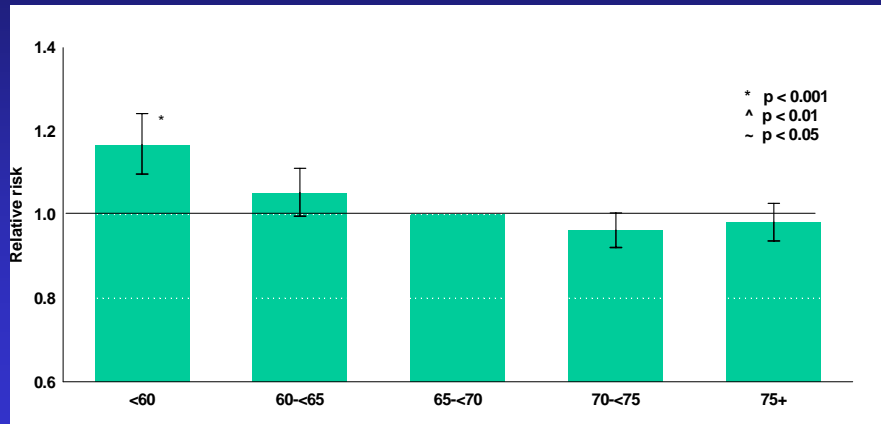
Effect on Ultrafiltration of changes in dialysate volume, dwell time, and [glucose]



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 - 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

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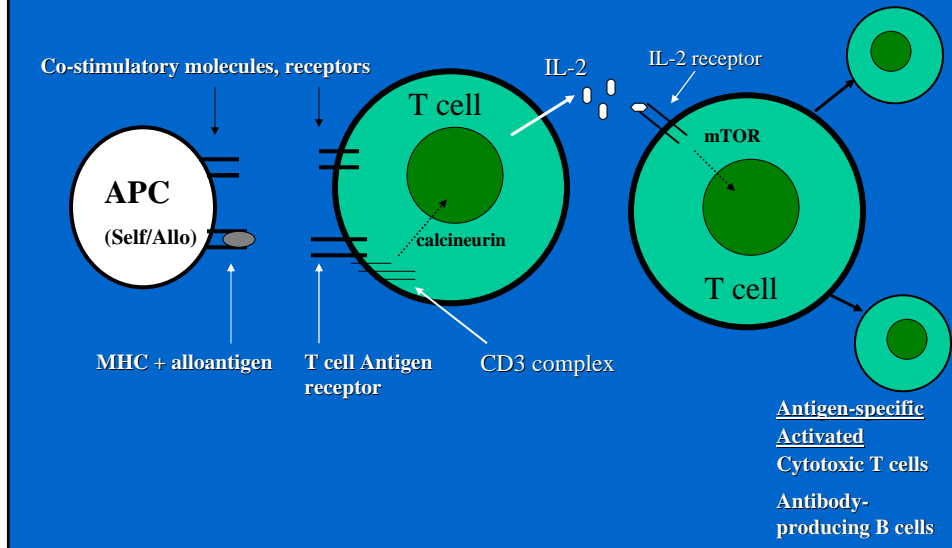
- **199 Transplants 2005**
  - 93 (47%) Deceased Donor
  - 106 (53%) Living Donor
    - 65% Living Related donor
    - 35% Living-Unrelated Donor (Spousal, Friends)

## 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)

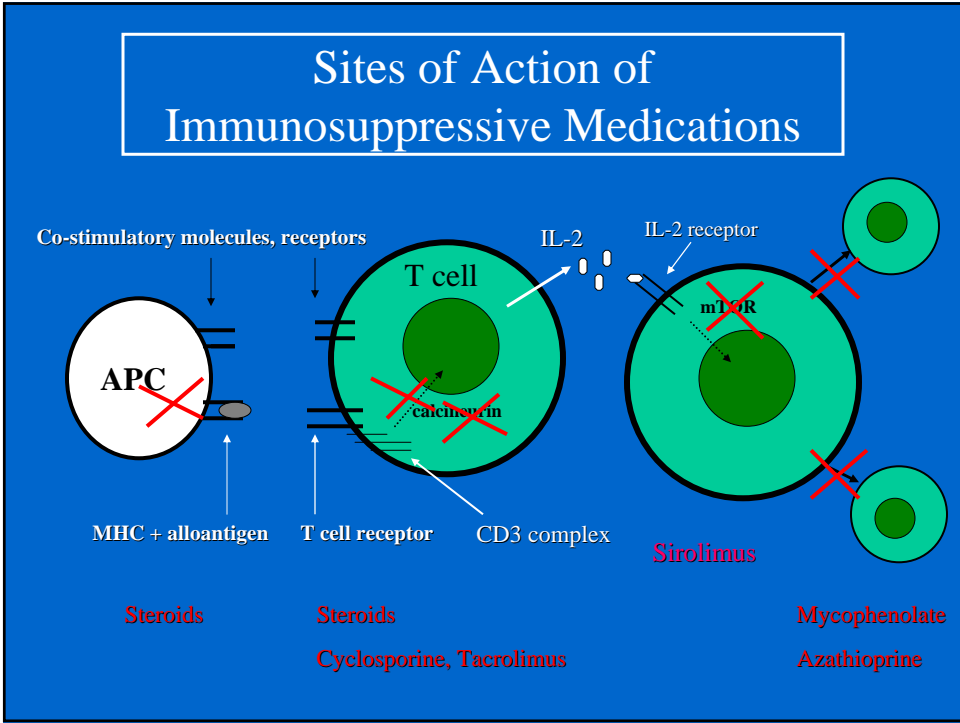


## Allo-Immune Activation



## 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



### Maintenance Immunosuppressive Regimens

Triple Therapy

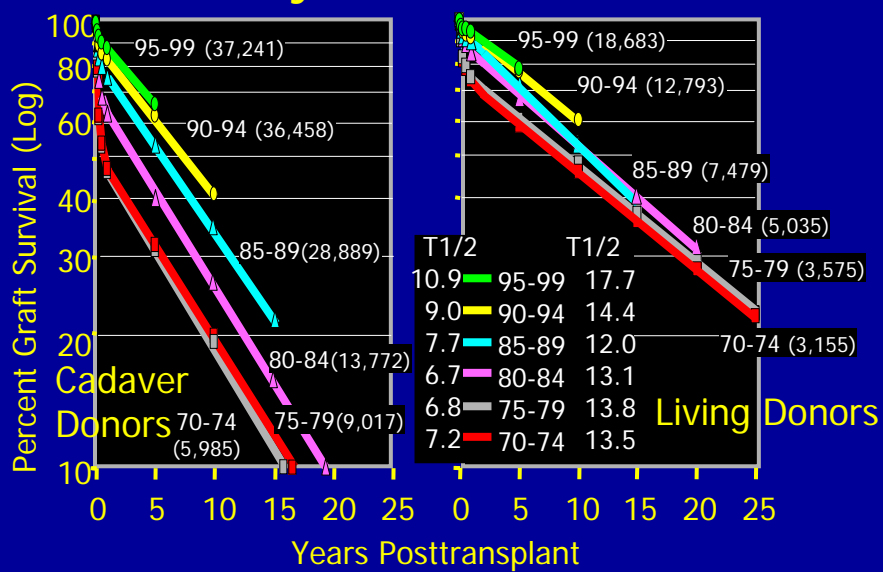
Cyclosporine/ Tacrolimus	+	Mycophenolate	±	Prednisone
Cyclosporine/ Tacrolimus	+	Sirolimus	±	Prednisone
Sirolimus	+	Mycophenolate	±	Prednisone

## Current Renal Transplant Survival Rates

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

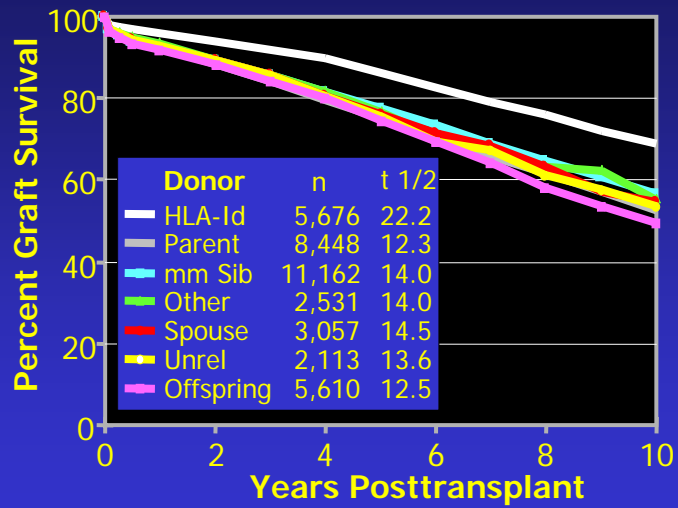
SRTR 2005 data

## Kidney Graft Survival Rates



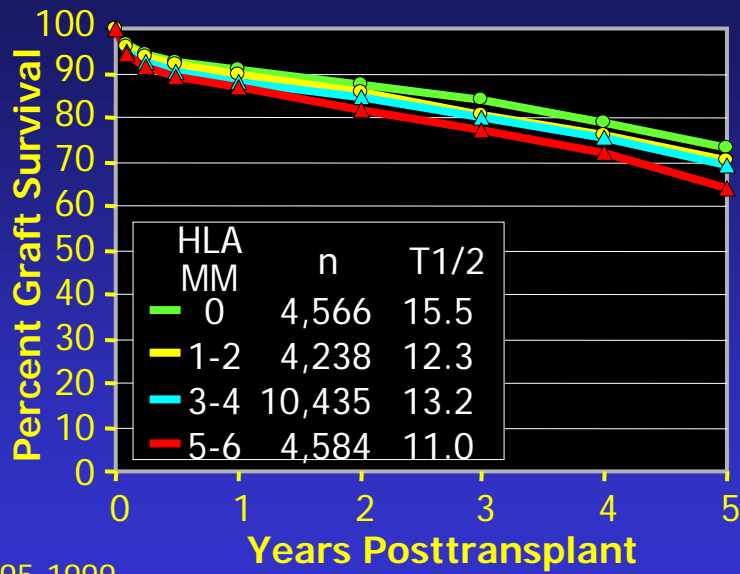
*Cecka, Clinical Transplants 2000 (p. 2)*

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



*Cecka, Clinical Transplants 2001 (p.4)*

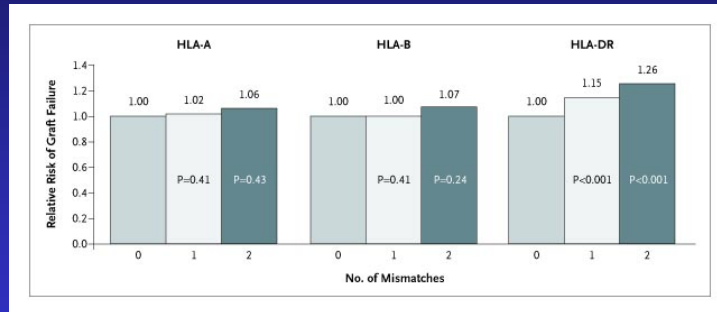
## Effect of HLA Mismatches on Graft Survival



1995-1999

*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



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

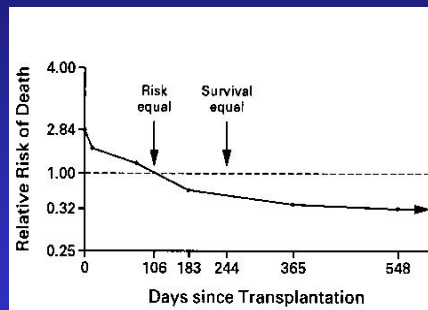


Figure 2. Adjusted Relative Risk of Death among 23,275 Recipients of a First Cadaveric Transplant.

Wolfe, et al *NEJM*, 1999

## Survival: Transplant vs Dialysis

### Relative mortality risks

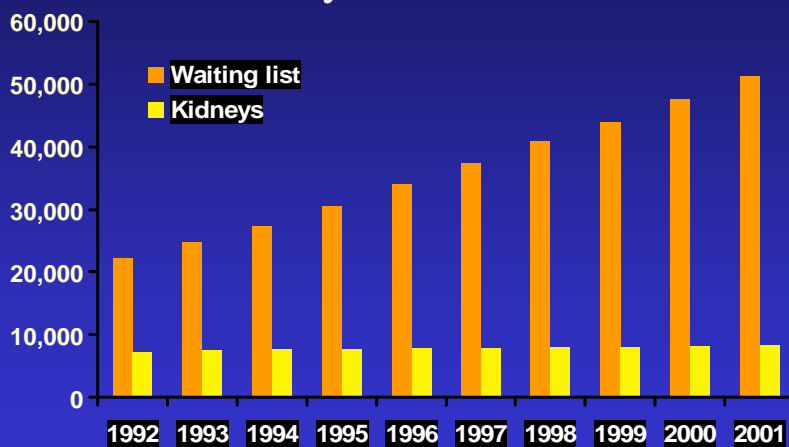
<i>Dialysis - Wait List (WL) vs non-Wait List:</i>	<i>RR</i>	<i>0.43-0.55</i>
Transplant vs WL Dialysis: (1st 2 wks)	RR	2 - 5
Transplant vs WL Dialysis: (146 -377 d)	RR	1
Transplant vs WL Dialysis: (long-term)	RR	0.26 - 0.41

Wolfe et al, USRDS Database, 1998 ASN

## Challenges to Long-Term Success of Renal Transplantation

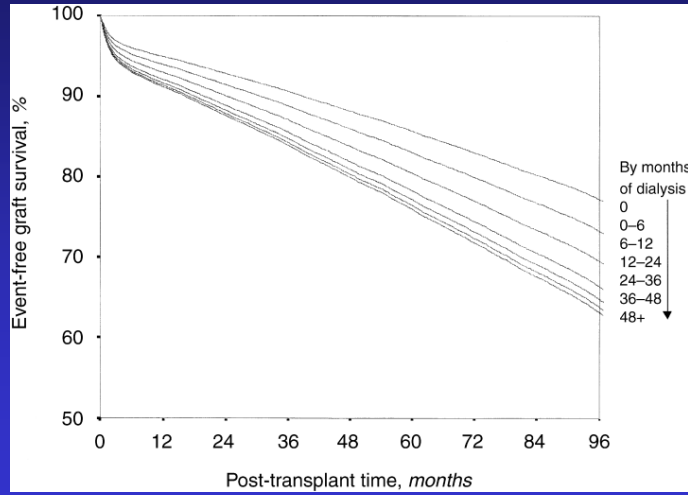
- Donor Shortage
- Chronic Allograft Nephropathy
  - Long-term progressive deterioration in renal function
- Patient death
  - Cardiovascular disease
  - Complications of Long-term Immunosuppression
    - Malignancy
    - Infection

### The US waiting list for deceased donor kidneys - 1992–2001



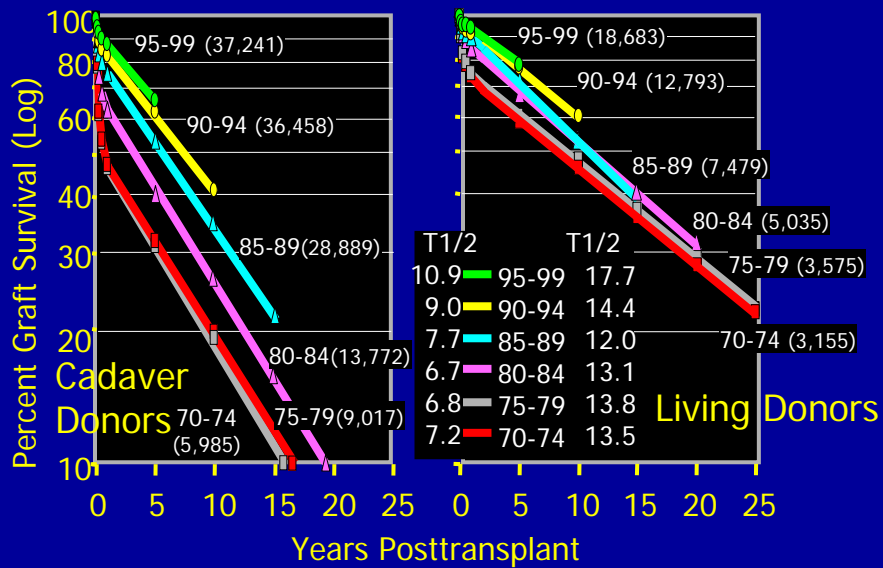
SRTR 2002

## 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