Overview of Kidney Transplantation

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Topics

1. History of Transplant
2. Treatment options for Chronic Kidney Disease (CKD)
3. Compatibility
4. Wait List
5. Benefits and Risks of Transplantation
6. Types of Kidney Donors
7. Alternative Programs for Living Donation
8. Rejection
9. Immunosuppression
Transplant History

- **1910** - ABO blood grouping identified.
- **1940’s** - Histocompatibility – understand tissue compatibility
- **Early 1954** - Cortisone-like medications
- **1954** - 1st successful living donor transplant
  - Identical twin brothers in Boston
- **1957** – Human Leukocyte Antigen (HLA)
- **1960s** – Azathioprine (Imuran®), Prednisone
- **1980s** – Cyclosporine, OKT3®
- **1990s** – Prograf®, Cellcept®, Neoral®, Monoclonal antibodies, Rapamune®, Thymoglobulin®
- **2000s** – Generic Neoral, Myfortic®
OPTN
Organ Procurement and Transplantation Network

The unified transplant network established by the United States Congress under the National Organ Transplant Act (NOTA) of 1984.

www.optn.org

UNOS
United Network for Organ Sharing

The organization contracted to administer the OPTN. Established 1986.

www.unos.org

UNOS has also developed a website specifically for patients and families at www.transplantliving.org

(For Spanish version: www.transplantesyvida.org)
UNOS

- Mission to improve the effectiveness of organ donation, procurement, distribution, and transplantation.
- Establishes regulations and policies relating to transplant
- Responsible for equitable distribution of all organs
- Charged with increasing organ donation
- Supervises compliance with policies for identifying potential organ donation, sharing, matching, and distribution of organs
- Transplant center must be member of UNOS to receive Medicare/Medicaid benefits

OPO

Organ Procurement Organization

- An OPO is a program that acquires and coordinates placement of donated organs for patients on national transplant waiting lists.
- The New Jersey Organ and Tissue Sharing Network
  - The non-profit, federally certified organ procurement organization (OPO) for New Jersey.
  - [www.sharenj.org](http://www.sharenj.org)
Other Web Resources

- American Kidney Fund: www.kidneyfund.org
- American Society of Transplantation: www.a-s-t.org
- National Kidney Foundation: www.kidney.org

The Past

Renal Failure in the 1950s:

- No dialysis
- Transplant success rate 10-20%
  - No immunosuppression
  - Immunology not understood
- ESRD = Death
Bones can break, muscles can atrophy, glands may loaf and even brains can go to sleep

but if the kidney fails neither the bones, muscles, glands nor the brains can carry on!

*William Osler MD*

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**In just over 50 years …**

- **1954** 1st successful living donor transplant
  - Identical twin brothers in Boston

- **1980’s** Transplant success rate 70% - 80%

- **2006** Transplant success rate 96% at 1 year
What happened?

- Drug Development
- Understanding of Immunology
- Advances in medicine and surgery
- Dialysis available

Major causes of End Stage Renal Disease (ESRD)

- Diabetes mellitus (DM)
- Glomerulonephritis (GN)
- Hypertension (HTN)
- Developmental/congenital disorders: polycystic kidney disease (PKD)
- Collagen Vascular Disorders: Lupus, Scleroderma etc
- Obstructive disorders
Challenges of Living with ESRD

- Multi-organ problems
- Decreased Quality of Life
- Decreased Life Expectancy – even on dialysis

Treatment Options: Transplant

Allograft

A graft transplanted between two genetically different individuals of the same species
Treatment Options: Transplant

Living Donor Types:

- Compatible Donor
  - Blood related
  - Emotionally related
  - Altruistic

- Incompatible Donor
  - Kidney Exchange Program
  - Program for Incompatible Transplant

Deceased Donor Types:

- SCD-Standard Criteria Donor
- ECD-Expanded Criteria Donor
- DCD-Donation after Cardiac Death
Kidney Wait List Vs. Transplants


Decreased Organ Donation
- Improved trauma care
- Public awareness of speeding
- Drunk-driving penalties
- Safer motor vehicle provisions [Seatbelts, airbags, motorcycle helmets]
- Medical Exclusion
- Actual consent rate 50-60%

Increasing Waiting List
- High Success Rates
- New ESRD Patients: Elderly
- Diabetics
- Retransplants
- Multiorgans
- Pediatrics
Benefits of Transplantation

- Increased life expectancy compared to those who remain on dialysis
- Diabetic patients live longer with a transplant than on dialysis
- Enhanced quality of life due to improved health and energy
- Benefits vary based on age and other medical conditions of the transplant patient

One Year Kidney Transplant Survival

- 1988: Deceased Donor Kidney - 75, Living Donor Kidney - 88
- 2007: Deceased Donor Kidney - 90, Living Donor Kidney - 96
Projected Years of Life from Waitlist
Waitlist Dialysis vs. Transplant Patients by Age Group

Projected Years of Life

- 20-39
  - Wait List Dialysis: 14
  - Transplant: 31

- 40-59
  - Wait List Dialysis: 11
  - Transplant: 22

- 60-74
  - Wait List Dialysis: 6
  - Transplant: 10

Projected Years of Life from Waitlist
Waitlist Dialysis vs. Transplant Patients
Diabetic vs. non-Diabetic (Age 40-59)

Projected Years of Life

- Non-Diabetic
  - Kidney Wait List & on Dialysis: 12
  - Transplanted: 19

- Diabetic
  - Kidney Wait List & on Dialysis: 8
  - Transplanted: 22
Transplant Referral Process

- Treatment options discussed with the patient and family
- Referral to a transplant center
- Verification of insurance coverage with selected transplant center
- Recipient medical evaluation
- Presentation to multidisciplinary Transplant Team to review evaluation findings and potential candidacy
- If approved, placed on wait list or proceed with live donor transplant

Transplant Candidate Evaluation Goals

- Determine
  - health status
  - needed testing and/or treatment
  - any social and/or emotional problems

- Ways to improve patient health status

- Determine if patient can be safely transplanted
Evaluation of renal transplant candidates

- Ideally, pre-modality (before dialysis)
  - Many patients are evaluated after they start dialysis
- Transplant when creatinine clearance < 20 cc/min
  - Systemic problems not manageable without treatment
- Evaluation process
  - Patient education
  - Evaluation by transplant team
    - Physician
    - R.N. Transplant Coordinator
    - Social Worker

Evaluation Overview

- Renal Disease
- Renal Function
- Cardiovascular
- Urologic
- Pulmonary
- Endocrine
- Infectious Disease
- Malignancy
- Coagulation problems
- Psychosocial / Insurance
- Age
Contraindications to Renal Transplantation

- Cancer
- Active Infection
- Advanced Cardiac Disease
- Psychosis
- Advanced Liver Disease

Selection Criteria

- Every transplant center sets its own criteria for inclusion, exclusion and evaluation process
- CrCl < 20 mL/min. is needed to accrue waiting points per United Network of Organ Sharing (UNOS) policy
- Estimated glomerular filtration, eGFR, is increasingly being used as a more accurate indicator of residual renal function*
- Age is relative to physiological status
- Financial resources need to be addressed

*http://www.kidney.org, search “eGFR”
Recipient Evaluation
Pre-Transplant

- History and Physical
- Psychosocial evaluation
  - Social support systems
  - Functional status/ADL
  - Financial resources, insurance
  - Work history; employment status, eligibility for Medicare
  - Adaptation to ESRD, dialysis, coping style
  - Adherence to current regime
  - Alcohol and drug use/abuse

Recipient Evaluation
Pre-Transplant

- Review of complete history and physical
  - Cardiovascular disease
  - Infectious diseases
  - Malignancy
  - Urologic evaluation
  - Obesity
  - Dental examination
  - Current on all routine health screening
- Ability to follow complex regimen
- Psychosocial stability
- Insurance coverage
Transplant Evaluation: Cardiovascular

- EKG
- Echocardiogram with history of hypertension, cardiac disease, or diabetes
- Chemical stress test if indicated by age, medical history
- Cardiac catheterization if indicated by positive stress test or center’s criteria
- Doppler studies – carotids/lower extremities if indicated

Pre-Transplant Cardiovascular Evaluation: Patients with Diabetes

All patients:
- Vessel studies-carotid and lower extremities
- Vascular consult if vessel studies positive

< 45 years old
- EKG
- Echo with ejection fraction
- Stress test or nuclear stress test if MI or family hx of MI at age 45-55

> 45 years old
- Same as < 45 years old plus chemical nuclear stress test
Transplant Evaluation: Infectious Diseases

- Viral/fungal titers may include:
  - CMV
  - Toxoplasmosis
  - Epstein-Barr (EBV)
  - Varicella, herpes
  - Hepatitis A,B,C
  - HIV
  - VDRL – confirmatory test if positive

- Evaluate for other underlying infections, e.g. UTI, pneumonia, abscessed teeth, check feet of patients with diabetes

Transplant Evaluation: Metabolic/Endocrine

- Blood glucose monitoring, HgbA1C
- Referral to Endocrinologist/Diabetes Clinic for optimal glucose control pre-transplant
- Diabetes co-morbidities
- Secondary hyperparathyroidism
- Lipid profile
Transplant Evaluation: GI/Liver

- Stool guiac
- Gall bladder or upper abdominal ultrasound
- Sigmoidoscopy, colonoscopy or barium enema if ≥50 y.o. or family history of colon cancer or symptomatic
- Hepatologist evaluation if history of hepatitis or abnormal liver function tests (LFT)
- Patients with long term diabetes: assess gastric emptying

Transplant Evaluation: Pulmonary

- Chest X-ray
- PPD testing
- Pulmonary function test if indicated
- Determine smoking history
  - (some centers will not transplant patients who smoke)
Transplant Evaluation:

Urinary Tract

- Assessment for recurrent urinary tract infections, ureteral reflux, bladder dysfunction, congenital anomalies of GU tract
- Voiding cystourethrogram (VCUG) and post void films in patients producing urine (if indicated)
- Referral to urologist for urological concerns
- Evaluate need for native nephrectomies

Recipient Evaluation

Pre-Transplant: Optional per Patient Need

- Pharmacologic stress test
- Echocardiogram
- Coronary angiogram
- Noninvasive vascular studies
- Women
  - Mammogram - ≥ 40 years old
  - PAP smear
- Men – PSA ≥ 45 years old
- Colonoscopy - ≥ 50 years old
Monthly Blood Specimen

Once patients is ACTIVE on wait list:

- A new blood sample is required every month to be sent to the Sharing Network Lab

- The blood sample is used to perform a cross match with deceased donor kidney if your name comes up on the list

- If NO sample - NO cross match - NO TRANSPLANT!

The Wait List

- A LIST is created only when an organ becomes available through donation

- List based on blood group of donor

- Points are determined by:
  - Time active on wait list
  - Number of HLA matches 1-6
  - PRA greater than 80%
  - Pediatric (less than 18 yrs old)
The Wait List

- Patient with the most points will be on top of the list and then:
  - A current blood sample must be available at the Sharing Network
  - Patient must be healthy, with testing up to date
  - Cross match must be negative
  - RN must be able to contact patient within 60 minutes!

Treatment Options: Transplant

Living Donor Types:

- Compatible Donor
  - Blood related
  - Emotionally related
  - Altruistic

- Incompatible Donor
  - Kidney Exchange Program
  - Program for Incompatible Transplant
Traditional Types of Living Donors

1. Living Related or Unrelated Kidney Donation
   - Genetic Related donors
     - father, mother, sister, brother, aunt, uncle
   - Emotional related donors (LURD, ERD)
     - husband, wife, friend

Alternative Types of Living Donors

2. Altruistic Living Donation
   - Directed
     - No genetic or emotional relationship
   - Non-Directed
     - Anonymous, no relationship

3. Living Donor Kidney Exchange Program
   - Exchange between incompatible pairs

4. Incompatible Transplant Program
   - Blood Type
   - + Flow crossmatch
Why Living Donation?

- In U.S. since 2001 – more living donations than deceased donations
- Living kidney transplants usually last about twice as long as deceased donor transplants
- Quality of the kidney is excellent
  - decreased rates of rejection
  - lower blood levels of immunosuppression required
  - decreased side effects and secondary illnesses

Who can be a living donor?

- Voluntary
- Altruistic
- Healthy
- Able to give informed consent
- Normal kidney function (2 kidneys)
- Medical clearance
- Psychosocial clearance
- Age: 18 – 70 +
**Absolute Contraindications to Donation**

- Diabetes
- Hypertension
- Renal impairment and/or urologic abnormality
- Liver Disease
- Active infection
- Chronic illness or infection
- Strong family history
  - Diabetes
  - Familial renal disease

**Advances in living donation**

- Laparoscopic nephrectomy
- Less invasive
  - Decreased infection, pain, complications
- Anesthesia extremely safe
- Hospital stay: 2 days
- Pain Management advances
- Able to drive a car 5-7 days post donation
- Back to work 7 to 10 days
The Gift of Donation

- **The gift of kidney donation**
  - Is a life-enhancing “gift”
  - Will dramatically improve the quality of that person’s life.

- **Motivation**
  - free from undue pressure or monetary compensation.
  - participation is completely voluntary
  - free to withdraw your decision to donate at any time.

- **Alternatives**
  - decision is NOT a matter of life and death
  - person with kidney failure have other alternatives including dialysis and waiting for a deceased donor organ.
### Blood Type Compatibility

<table>
<thead>
<tr>
<th>Recipient</th>
<th>Donor must be</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood type A</td>
<td>A or O</td>
</tr>
<tr>
<td>Blood type B</td>
<td>B or O</td>
</tr>
<tr>
<td>Blood type O</td>
<td>O</td>
</tr>
<tr>
<td>Blood type AB</td>
<td>A or B or AB or O</td>
</tr>
</tbody>
</table>

Incompatible recipient and donors are referred to:
- The Kidney Exchange Program
- The Program for Incompatible Transplants

### Crossmatch

- **Basic concepts of HLA: Human Leukocyte Antigens**
  - Unique protein marker code on cell surfaces
  - How your body knows its you
  - When exposed to another’s protein markers
    - Make antibodies
    - Will be incompatible with another human who has those proteins you have been exposed to before
  - PRA %: chance of not matching
Panel Reactive Antibody: PRA

- Previous exposure to genetic material through:
  - Blood transfusion
  - Pregnancy
  - Previous transplant
- Reported as percentage: PRA %
  - The higher the percentage, the harder to find compatible donor

Cross Matching

- Donor and recipient blood cells are mixed together in lab
- Check for reaction of recipient to donor’s HLA

2 Types of Crossmatches
- Crossmatch (Complement dependent lymphocytotoxicity assay)
  - LOW Sensitivity
- Flow Crossmatch (Flowcytometry assay)
  - HIGH Sensitivity
Incompatible Living Donors

- There are two programs available for recipients and their incompatible living donors
  - Living Donor Kidney Exchange
  - Program for Incompatible Transplants

Living Donor Kidney Exchange Program (LDKEP)

How does it work?
In the first pair, Recipient 1 is not compatible with Donor 1, and in the second pair, Recipient 2 is not compatible with Donor 2.

However, Donor 1 is compatible with Recipient 2 and Donor 2 is compatible with Recipient 1.
Evolution of Kidney Exchange

Traditional Paired Exchange

Two Pair Exchange

Three Pair Exchange

Chains

Non Directed Altruistic Donor

Cluster #1

Cluster #2

Cluster #3

Etc.

3 Pair Exchange

Donor: Friend
Blood Group: B

Donor: Wife
Blood Group: AB

Recipient: Pre HD
Blood Group: A

Recipient: Dialysis
Blood Group: B

Recipient: On Waiting List
Blood Group: AB

Boston

SBMC

SBMC

SBMC
Program for Incompatible Transplants

- Types of Incompatible Transplants
  - Blood Group Incompatible
  - Tissue Type (crossmatch) incompatible

- Excellent success rates – almost comparable to compatible transplant rate

Compatible Blood Groups

<table>
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</tr>
<tr>
<td>Blood group B</td>
<td>B or O</td>
</tr>
<tr>
<td>Blood group O</td>
<td>O &amp; maybe A2</td>
</tr>
<tr>
<td>Blood group AB</td>
<td>A or B or AB or O</td>
</tr>
</tbody>
</table>

A: 20% are A2 subtype
80% are A1 subtype
Blood Groups: New Science

- We have antibodies against other blood groups
  - O’s have Anti-A and Anti-B antibodies
  - A’s have Anti B-antibodies & B’s have Anti-A antibodies
- Measured in titers
  - Titer 1:2, 1:4, 1:8, 1:16, 1:32 doubles each time...
  - 1:32 stronger then 1:16
  - How many times does it take to wash out the antibody?
- Antibodies removed by plasmapheresis & IVIG
  - Typically 4 pre-op and 3 post-op
- A2 blood group very similar to O blood group
  - Almost a compatible transplant in some cases

Patient Education

Kidney Exchange or Incompatible Transplant?

- Blood group incompatible transplants
  - It is may be now possible to overcome in the blood group barrier
    - Especially A2 donor to O recipient
- Crossmatch incompatible transplants
  - some Positive crossmatches can be overcome
- Kidney Exchange for Compatible transplant
- What is the right treatment option?
  - Incompatible or Exchange?
Treatment Options: Transplant

Deceased Donor Types:

- SCD-Standard Criteria Donor
- ECD-Expanded Criteria Donor
- DCD-Donation after Cardiac Death

Deceased Donors

A deceased donor organ comes from someone in the hospital who is seriously ill and who will not recover.

Next of kin must consent to organ donation.
Standard Criteria Donor

- Age 59 or younger
- Brain dead
- Does not meet criteria for Expanded Criteria Donor

Expanded Criteria Donor (ECD)

- Donor age 60 or older
- Donor over age 50 with medical history of 2 of the 3 conditions:
  - History of medication controlled high blood pressure
  - Cause of death was Stroke
  - Creatinine level greater than 1.5
General Organ Risk Factors

- Risk of contracting an infectious disease
- Donor’s medical or social history
- Condition or age of the organ used

Pre-Operative Care

- Dialysis may be indicated
  - Assess fluid status for volume overload
  - Check electrolytes
    - Hyperkalemia $\geq 6.0$ mg/dL may delay surgery
- Dialysis may enhance platelet aggregation and coagulation intra & post-operatively
The transplant operation

- Transplanted kidney can be placed on either side
- Pocket is made for kidney in retroperitoneal space

May 09
One Donor

- 2 Kidneys
- Pancreas
- Heart
- Liver
- 2 Lungs
- Bowel
- Corneas
- Bone

Nicholas Effect

Surgical Risks and Complications

- Uncommon complications that may require surgical repair include:
  - Lymphocele: fluid collection around transplant
  - Surgical incision infection
  - Incision separation
  - Urine leak
  - Bleeding

- There is no guarantee that the transplanted organ will work immediately or at all. Some reasons include:
  - Delayed graft function
  - Clotting of transplanted kidney (1 - 2% risk)
Transplant Recipients Post Op

- Patients go to PACU
- From there:
  - Transplant Unit monitored bed or ICU
    - Hemodynamically unstable
    - Respiratory insufficiency
    - Require immediate anticoagulation
- Length of stay (on average)
  - Deceased donor transplant: 7-8 days
  - Living donor transplant: 5 days

Transplant Post Op Testing

- Renal Scan: demonstrates
  - blood flow to the graft
  - Urine flow
  - Presence of any urine leaks
- Renal Ultrasound: demonstrates
  - Hydronephrosis
  - Fluid collections around graft (subscapular collections)
- Doppler Study: demonstrates
  - Blood flow in the renal vessels
Post Operative Care

Assess renal function

- Urinary catheter in for 2-5 days, *never clamp!*
- Measure urine accurately
- ↓ urine output may indicate
  - Delayed graft function (DGF)
  - Urine leak
  - Rejection
  - Clot occluding ureter or catheter
- ↓ intravascular volume
- Graft thrombosis
- Monitor BUN, Cr

Assess fluid status for deficit or excess

- Maintain accurate I&O and teach pt to do
- Daily weights at same time of day
- Assess breath sounds for crackles
- Monitor CVP, BP, pulse rate
- Look for peripheral or sacral edema
- Check skin turgor, concentration of urine, dry mucous membranes
- Hypotension could compromise blood flow to the graft
Post Operative Care

- Monitor Potassium (K⁺) levels
  - Delayed graft function (DGF) may ↑ K⁺
  - Cyclosporine or Tacrolimus may cause ↑ K⁺
  - Excess urine output or loop diuretics may cause ↓ K⁺
  - ↑ or ↓ K⁺ may cause arrhythmias; patient may be on cardiac monitor for observation

- Monitor other laboratory tests
  - Calcium, phosphorous, magnesium and signs of any electrolyte imbalance
  - Patients may actually become hypophosphatemic
  - Immunosuppressive drug levels

- Blood glucose
  - ↑ with steroid administration in patients with or without known diabetes
  - Glycemic control important to minimize post-operative complications
Post Operative Care

- Maintain circulatory function
  - Frequent monitoring of vital signs
  - Check femoral, popliteal & pedal pulses
  - Assess cardiac status
  - Facilitate leg exercises and early ambulation
  - Use pneumatic compression stockings if patient is non-ambulatory

Post Operative Care

- Maintain pulmonary function
  - Monitor O₂ sats (keep ≥93%); incentive spirometer, early ambulation, TCDB
- Prevent infections
  - Meticulous hand hygiene & care of IV lines, catheter, PD catheter, wound
  - Aggressive pulmonary toilet
  - Nurses should not care for other patients with infections
- Provide adequate pain control, assess effectiveness
- Monitor bowel sounds/function
- Provide and monitor immunosuppressant regimen as ordered
Medical complications

- Rejection
- Delayed graft function
- Medication side effects
- Infection:
  - Wound
  - Urinary tract
  - Lungs

Medical Complications

- Acute rejection:
  - the recipient’s immune system recognizing and attacking the donor organ
- Serum Creatinine: monitor kidney function
- A biopsy is the best way to diagnose rejection
- Almost all acute rejection episodes are successfully treated with medication
Long Term Complications

- Chronic Rejection: long term slow rejection: known as Chronic Allograft Nephropathy
- Return of original kidney disease (only certain diseases have risk of returning)
- Diabetes: risk caused by some medications – influenced by patient medical history
- Complications related to long term anti-rejection medication (immunosuppression)

Types of Rejection

- **Hyperacute rejection**: Minutes to hours, Not reversible/very rare occurrence
- **Accelerated acute**: Within 2 to 4 days, May be reversible
- **Acute**: Weeks, Reversible
- **Chronic**: Slowly progressive months to years, Not reversible/common occurrence
Transplant Acute Rejection

- Higher risk - first 3 months post transplant
- Usually only symptom – increased creatinine
- Easily diagnosed with biopsy
- Reversal rate 97-99 %

Immune Mechanisms in Rejection

- Antibody Mediated Rejection
  - Recognition of foreign HLA
- Cellular Mediated Rejection
  - T Cell activation
  - 3 signal model
**Goals Of Immunosuppression**

- Prevent rejection
- Maintain long term patient and graft survival
- Minimize drug induced toxicity

**Understanding of Immunology leads to drug development**

Central Issues

- Prevention and treatment of:
  - allograft rejection
  - complications of immunosuppression

Immunosuppression

- More immunosuppression given
  - Less allograft rejection
  - Weaker immune system

- Less immunosuppression given
  - More allograft rejection
  - Stronger immune system

Complications of immunosuppression

- More infections
- More cancers
- More medication side effects

- Fewer infections
- Fewer cancers
- Fewer medication side effects

Immunosuppressive Regimens

- Is the individual at high or low risk for rejection?
- Is the individual at risk for having delayed graft function?
- Does the individual have a particular susceptibility to a side effect of a certain medication?
Classic Regimen

- Induction for high risk patients only: potent anti-T cell antibody preparations to prevent rejection in high risk patients
  - Thymoglobulin
  - OR
  - Simulect

- Maintenance Immunosuppression for all patients
  1. Steroids (prednisone)
  2. Calcineurin inhibitors (cyclosporine and tacrolimus)
  3. Mycophenolate mofetil or Sirolimus

Factors Increasing the Risk of Rejection

- African American race
- Elevated Panel Reactive Antibodies (PRA)
- Pediatric Patients
- Long Cold Ischemic Time
- High HLA mismatch
- Relationship in living donation situations
  - Husband to wife (if had children together)
Induction for Delayed Graft Function

- DGF increases the risk for rejection

- The use of potent anti-T cell antibody preparations to prevent rejection and delay the introduction of calcineurin inhibitors
  - Calcineurin inhibitors cause renal vasoconstriction resulting in delayed recovery from ATN in patients with DGF

Thymoglobulin

- Polyclonal antibody against various T cell surface markers (including CD3): targets signal one

- Uses:
  1) Induction immunosuppression for high risk patients
  2) Allows one to delay the introduction of calcineurin inhibitors in new transplants with ATN
  3) Treatment of moderate-severe rejection
Thymoglobulin

- Side effects
  - 1st dose reaction (prevent with pre-medication of Tylenol, Benadryl and Steroids)
  - Leukopenia
  - Thrombocytopenia

Simulect (basiliximab) or Zenapax (daclizumab)

- IL2 Receptor Blockers used for induction
  - Simulect given as 20mg on day 0 and 4
  - Zenapax given 1 mg/kg intraop and q2wks x 4

- Side effects:
  - Very well tolerated
  - 1st dose reactions very rare
  - Much lower rate of leukopenia/thrombocytopenia than thymoglobulin
Corticosteroids

Dosing: 500mg IV initially then tapering to Prednisone 5mg day maintenance dose

Drug levels: not done

Corticosteroids

Side Effects:
- Mood swings/insomnia
- Acne
- Edema
- Hyperglycemia
- Hypertension
- Hirsutism
- Cushingoid facial appearance
- Cataracts
- Bone disease: Osteoporosis, AVN
- Steroid induced psychosis (with initial high dosing)
Calcineurin Inhibitors

- **Cyclosporine** (Neoral, Gengraf, Sandimmune)
  - Inhibits calcineurin. Calcineurin is a phosphatase needed for IL-2 synthesis.
- **Tacrolimus** (Prograf, FK506)
  - Forms a complex with FK-binding protein which subsequently inhibits calcineurin
- Both inhibit signal one

Dosing: dosed according to 12 hour trough levels

Drug levels: Goal trough levels depend on several factors including:
- Time from transplantation (higher levels immediately after transplant)
  - Cyclosporin range 100-400 ng/mL
  - Tacrolimus range 5-15 ng/mL
- Other immunosuppressive medications being used
### Calcineurin Inhibitors Side Effects

- Acute renal dysfunction mediated by renal vasoconstriction
- Chronic nephrotoxicity
- **Hypertension** (Cyclo > Tacro)
- Hyperlipidemia (Cyclo >> Tacro)
- **Pancreatic islet cell toxicity** (Tacro >> Cyclo)
- Alopecia (Tacrolimus)
- Hirsutism (Cyclo)

### Calcineurin Inhibitors Side Effects

- Hyperkalemia
- Hypomagnesemia
- Hyperuricemia (Cyclo > Tacro)
- Tremor (Tacro >> Cyclo)
- GI disturbances (Tacro >> Cyclo)
- Gum Hypertrophy (Cyclo > Tacro)
- HUS type picture
- Rhabdomyolysis (especially in conjunction with statins)
Drugs Which Decrease Calcineurin Metabolism (increase levels)

- Metabolized by cytochrome P450 system found in liver and GI tract
  - Diltiazem and verapamil (raise by up to 40%)
  - Ketoconazole > itraconazole > fluconazole > voriconazole (ketoconazole may raise by up to 80%)
  - Macrolides (especially erythromycin and clarithromycin. Azithromycin is generally safe to use without dose adjustments)
  - Others: amiodarone, grapefruit juice, saquanivir

Drugs Which Increase Calcineurin Metabolism (decrease levels)

- Dilantin
- Phenobarbital
- Tegretol
- Rifampin
- Isoniazid (much lesser extent than rifampin; preferred agent for TB prophylaxis in transplant pts)
- Nafcillin
- St. John’s Wort
Tacro or Cyclo?

- Both meds produce excellent short term patient and graft survival
- Several large studies have shown that Tacrolimus is associated with a lower incidence of acute rejection
  - In reality, choice of which medication is often based on side effect profile
  - One clear benefit of Tacrolimus is as rescue therapy for treatment of refractory acute rejection in patients on cyclosporine; substitution of Tacrolimus has shown reversal in up to 75% of cases

CellCept

(mycophenolate mofetil)

- Antiproliferative agent used along with calcineurin inhibitor
- CellCept selectively inhibits T and B lymphocyte proliferation
- Inhibits signal three
CellCept

- Usual Dosing: 1gm BID (1.5gm BID in African Americans)
- Drug levels: not routine but MPA levels are done in some centers
- Side effects:
  - Leukopenia
  - Anemia
  - Thrombocytopenia
  - GI symptoms (bloating, diarrhea, N/V); side effects are usually quickly resolved with transient reduction in CellCept dose
  - Myfortic is enteric-coated CellCept that may help reduce its GI side effects
- No nephrotoxicity

Prophylaxis

- Bactrim (TMP/SMX)
  - prevents pneumocystis
- Valcyte (valganciclovir)
  - prevents CMV
- Mycelex/Nystatin
  - prevents fungal infections
Steroid Free Protocols

- Increasingly being used for low-risk patients
- Most protocols use induction to provide adequate immunosuppression early on (highest risk of rejection is in the first few months post-transplant)
- Excellent short-term outcomes but no long-term follow-up yet