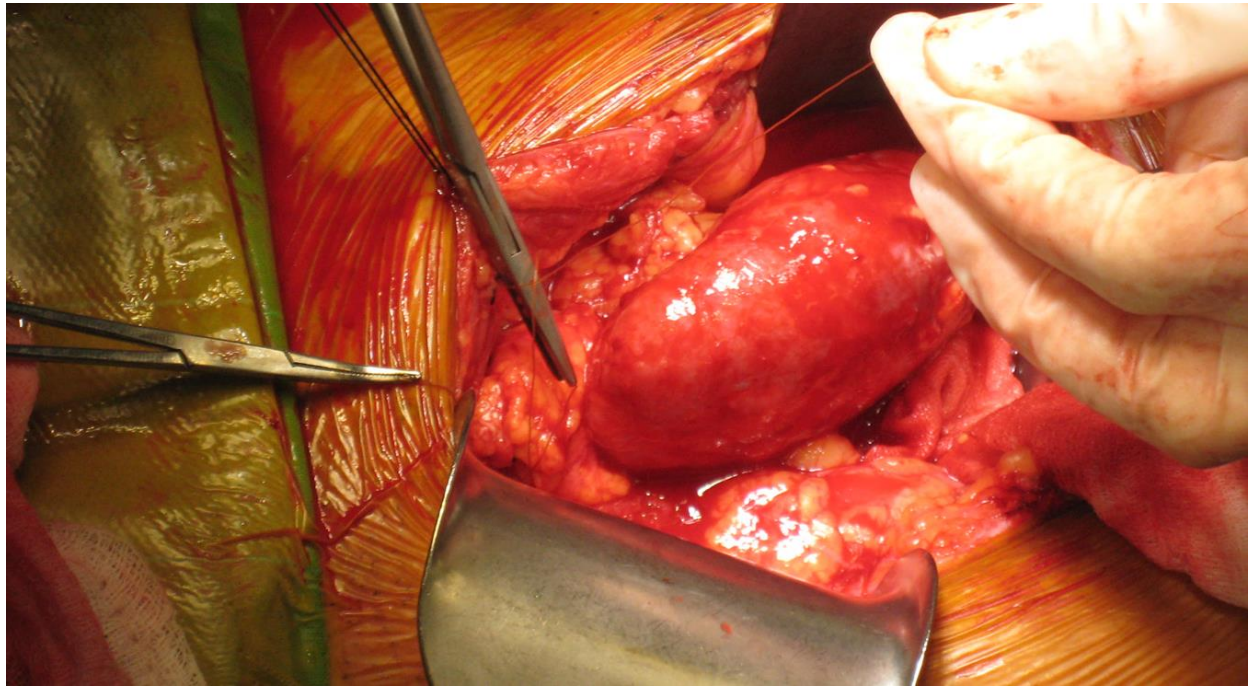
Anti-rejection Medications After Kidney Transplant



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Rejection

- Hyperacute rejection

  - occurs shortly after the reperfusion

  - recipient cytotoxic antibodies and complement react with donor vascular endothelial antigens

- Acute rejection

  - occurs approximately 5 days after organ transplant

  - S/S: graft pain, swelling, and fever

    urine output ⬇ serum creatinine ⬆

- Acute rejection (cont.)
  - Parenchymal blood flow ⬇
  - Gold standard test: Needle graft biopsy

- Chronic rejection
  - characterized by a gradual deterioration of kidney function
  - histologic features : interstitial fibrosis, arteriolar sclerosis, and tubular atrophy
  - may induced by drug toxicity

Immunosuppression Protocols

- Decreased risk for rejection
- Minimization of long-term side effects (Infection and cancer)
- Cost consideration

- Should be individualized for each patient and higher dosage in:
  - High levels of preformed antibodies
  - Delayed graft function
  - Previously transplanted
  - Poorly matched donors

Immunosuppression Protocols

- Currently, the most common protocols include
  - IV induction with antithymocyte globulin (ATG) or basiliximab
  - maintenance with tacrolimus, mycophenolate, and low-dose steroid

- Using these agents, biopsy-proved graft rejection rates are approximately 10% in the first year and mortality rates continue to improve

Immunosuppressive agents in induction therapy

- Depleting antibodies: antithymocyte globulin (ATG) , Alemtuzumab and Rituximab

- ATG blocks T cell membrane proteins and resulting in T cell depletion
- Alemtuzumab directed against CD52, thereby depleting T cells, B cells, NK cells and monocytes
- Rituximab directed against CD20, inducing B cell depletion

Immunosuppressive agents in induction therapy

- Non-depleting antibodies
- Humanized anti-CD25 monoclonal antibodies : Basiliximab (Simulect) and Daclizumab (Zenapax) , targeted alpha chain of the IL-2 receptor and block the IL-2 mediated responses
- Basiliximab pre-op 2 hr IVD 20 mg，and 2nd doage post-op 72 hr
- Prevent but not to treat the acute rejection
- Complement the effect of calcineurin inhibitors
- No side effects except cost issue

Immunosuppressive agents in induction therapy

- Intravenous immune globulins (IVIG)

- Pooled human gammaglobulin preparations
- Inhibit anti-HLA antibodies and produce long-term suppression of anti-HLA reactive T cells and B cells
- Reduce high levels of preformed anti-HLA antibodies in sensitized patients
- Treat acute humoral rejection and certain post-transplantation viral infection

Immunosuppressive agents in maintenance therapy

- Corticosteroids (Prednison and Methylprednisolon)
- Calcineurin inhibitors (CNI): Cyclosporine (CsA) and Tacrolimus (Tac)
- Mycophenolate mofetil (MMF) and Mycophenolic Acid (MPA)
- The mTOR inhibitors: sirolimus (Rapamune) and everolimus (Certican)

Corticosteroids

- First used to treat rejection in the 1960s
  - Inhibit the dendritic cells
  - Inhibit the transcription of cytokines genes and all the stages of the T- cell activation
  - Reduce the number of circulating lymphocytes, monocytes and eosinophils
  - Redistribution of lymphocytes from the vascular compartment to lymphoid tissue

- Used as
  - High doses pulses
  - Low dose maintenance regimen
  - Tapering oral dose over time

Corticosteroids

- Dosage example:
  - Pre-op methylprednisolone 1 gm IVD
  - Post-op hydrocortisone 100mg IVD，then tapering dose by days and shift to oral prednisolone within a maintain dose 5-10 mg/day by weeks

- Long-tern side effect:
  - Opportunistic infections
  - Cushing’s syndrome
  - Hyperglycemia, hypertension , dyslipidemia
  - Impaired wound healing
  - Osteoporosis

Calcineurin inhibitors

- Inhibits the activity of Calcineurin
  - Reduced activation of nuclear factor of activated T cells (NFAT)
  - Decreased cytokine production (including IL-2)
  - Diminished proliferation of T cells

- CsA enhances the expression of transforming growth factor-β (TGF-β) and may be responsible for the development of interstitial fibrosis, an important feature of CNI nephrotoxicity

Calcineurin inhibitors

- CNI are nephrotoxic
  - Enhancement of early post-transplant graft dysfunction
  - Dose related reversible renal vasoconstriction
  - Chronic interstitial fibrosis
  - Acute microvascular disease
  - Hypertension and electrolyte abnormalities

Calcineurin inhibitors
Cyclosporine

- Widely used after 1980 in transplantation
- Improving graft survival rate from 50 % to 88%

- Dosage example:

 - Initial dosage 6-18 mg/kg/day divided in two dosage
 - Tapering 0.5 mg per week
 - Maintain dose 5-10 mg/day
 - Monitor trough level (100-200 ng/ml in first month and 25-100 ng/ml in 12^{th} month)

- Side effect

 - Electrolyte abnormalities
 - Neurotoxicity
 - Hypertension

Calcineurin inhibitors
Tacrolimus

- Preferable to cyclosporine except in patients with DM
  - Better outcome in transplantation
  - Less nephrotoxicity
  - Glucose intolerance

- Dosage example:
  - Initial 0.1-0.3 mg/kg/day divided in two dose
  - Tapering within 3 to 6 month
  - Maintain trough level about 5-8 ng/ml in the first year

Mycophenolate mofetil (MMF) and Mycophenolic Acid (MPA)

- Mycophenolate mofetil (MMF) is a prodrug that is hydrolyzed to the active immunosuppressant mycophenolic acid

- Inhibition of T and B cell proliferation by blocking DNA synthesis
- Inhibits antibody formation and the generation of cytotoxic T cells
- Down-regulates the expression of adhesion molecules on lymphocytes and impairs their binding to vascular endothelial cells
- Treat ongoing rejection and to prevent development and progression of proliferative arteriolopathy, a critical lesion in chronic rejection

Mycophenolate mofetil (MMF) and Mycophenolic Acid (MPA)

- Adverse effects

- GI tract side effect such as diarrhea (30%), varying degrees of nausea, bloating, dyspepsia, vomiting (20%), esophagitis, gastritis.
- Hematological side effect like leucopenia, anemia or thrombocytopenia
- Dose adjustment reverse side effect

Azathioprine (Imuran)

- Imidazole derivative of 6-mercaptopurina
- Inhibits gene replication and consequently T-cell activation
- Adjunctive agent of CsA but discontinued in many programs after the MMF was introduced
- Prevents the acute rejection, not treatment of rejections
- The most important side effects are leucopenia and thrombocytopenia, occasionally hepatitis and cholestasis

The mTOR inhibitors: sirolimus (Rapamune) and everolimus (Certican)

- Inhibit mTOR and down-regulate cytokine-driven T cell proliferation
- Also inhibits immunoglobulin synthesis by B cells, antibody-dependent cellular cytotoxicity as well as natural killer
- The mTOR inhibitors do not produce acute or chronic reductions in GFR
- Maintenance therapy and administered with a tapering dose of CNI
  (Drug level monitoring)

The mTOR inhibitors: sirolimus (Rapamune) and everolimus (Certican)

- Delayed wound healing due to impaired response of fibroblasts to fibroblast growth factor
- Recommended not to start mTOR inhibitors immediately after transplant surgery

- Reducing the risk of cancer, particularly skin cancer

- Increased risk of infections, proteinuria, hyperlipidemia as well as leukopenia and thrombocytopenia

Summary of Target Organ/System for Toxicities of Immunosuppressant Therapy

Organ/System	CNS	GI	Kidney	Hema	Skin	Endocrine	Dyslipidemia	Wound healing
PREDNISONE	+	+	-	-	+	+	+	+
CYCLOSPORINE	+	+	+	-	+	+	+	-
TACROLIMUS	+	+	+	-	-	+	-	-
SIROLIMUS	-	-	-	+	-	+	+	+
AZATHIOPRINE	-	+	-	+	-	-	-	-
MYCOPHENOLATE	-	+	-	+	-	-	-	-

Summary of Mechanisms of Action in Immunosuppressants