Goal:
 Enhance understanding of the common primary maintenance immunosuppressants, including monitoring, side effects, drug interactions and relevant clinical issues of significance.

Objectives:
 Identify the common “first line” maintenance immunosuppressant’s and alternative medications.

 Recognize clinical issues related to specific immunosuppressant’s and potential side effects for patients.
The Immune System Exists to Protect the Integrity of Self

Immune Recognition

- Like Self
- Not like self

The Immune System Exists to Protect the Integrity of Self

Immunology in Kidney Transplants

- Immune system defends body against foreign substances (protects integrity of self)
  - Bacteria
  - Viruses
  - Transplanted tissues

- Goal with immunosuppression
  - Need to control body's immune system
  - Key component in promoting short and long term graft survival
Immunology in Kidney Transplants

- Immunosuppressive agents target different steps in rejection cascade.
  - Blocking T cell response
  - Activate other immunologic pathways

- Combing agents offers maximum protection

Overview of Immunosuppression

- Immunosuppressive agents
  - Induction
  - Desensitization
  - Primary immunosuppression
Induction Immunosuppression

- Strong medications – used immediately post transplant or in the setting of acute rejection
  - Alemtuzumab (Campath®)
  - Anti-thymocyte globulin (rabbit) (Thymoglobulin®)
  - Basiliximab (Simulect®)
  - Methylprednisolone (Solumedrol®)

Desensitization

- Allows high risk patients more successful outcomes
  - IVIG monthly
Primary (Maintenance) Immunosuppression

- Key to preventing rejection over the life of the transplant
- They are medications which will be used daily for the rest of an individual’s life to prevent rejection.
- Current approach typically utilizes tacrolimus for clinical protocols.
- Immediately following transplant immunosuppression levels are high to prevent rejection and reduced overt time as the graft stabilizes.

T-cell activation and proliferation

- Antigen presenting cell
- Calcineurin
- mTOR
- Map kinases
- Cytokines
- CD25
- CD28
- B7
- CD25
- IL2R
- Daclizumab/Basiliximab
- Sirolimus
- Mycophenolate Azathioprine
- Cell cycle
- G1
- G2
- S1
- G2
- M
- mRNA
- Calcineurin
- Steroids
- Cyclosporine
- Tacrolimus
**Tacrolimus (FK506)**  
*Prograf®, Hecoria®, Astagraf XL®, Sandoz®*

- Calcineurin Inhibitor
- Needs to be given at the same time every day (typically 12 hours, sometimes 8 hours for small children)
- Give the same way every day (with or without food)
- Monitor the brand of tacrolimus

### Tacrolimus

**Side Effects**
- Decreased magnesium levels
- Increased potassium
- Increased glucose
- Increased blood pressure
- Nephrotoxic
- Tremors
- Leg cramps
- Hair loss

**Important Notes**
- Agitate compound tacrolimus (must shake 5-10 sec. into each dose)
- NEVER give grapefruit or juices with grapefruit
- NEVER give fruit related to grapefruit
  - Pomelos
  - Tangelos
Cyclosporine (Gengraf®, Neoral®, Sandimmune®)

- Calcineurin inhibitor
- Needs to be given at the same time every day (typically 12 hours, sometimes 8 hours for small children)
- Give the same way every day (with or without food)
- Monitor the brand of tacrolimus
- Neoral and Sandimmune are different drugs. NEVER SWAP
Cyclosporine

Side Effects
- Decrease magnesium levels
- Increased potassium levels
- Increase blood pressure
- Increased glucose
- Nephrotoxic
- Headaches
- Tremors
- Body hair growth
- Swollen gums

Important Notes
- NEVER give grapefruit or juices with grapefruit
- NEVER give fruit related to grapefruit
  - Pomelos
  - Tangelos

Azathioprine

Diagram showing the interaction between antigen presenting cell, T-cell, and the signaling pathways involving Calcineurin, m-TOR, and cytokines like CD25.
Azathioprine (Imuran®)

- Antiproliferative agent
- Given once a day at the same time
- May be given with or without food—be consistent—may affect absorption
- When given with food may lessen GI symptoms

Azathioprine

Side Effects
- Nausea, vomiting
- Decreased appetite
- Low platelet count
- Low WBC
- Low RBC
- Headaches
- Dizziness
- Hair loss
- Rash

Important Notes
- Often used when patients do not tolerate MMF due to diarrhea.
**Mycophenolate**

- Antigen presenting cell
- Signal 1
- Signal 2
- Signal 3
- CD28
- T-cell
- Calcineurin
- mTOR
- mRNA
- Cytokines
- Cell cycle
- G1
- G2
- S1
- m-TOR
- Map kinases

**Mycophenolate (Cellcept®, Myfortic®)**

- Antiproliferative agent
- Give medication at the same time every day, 12 hours apart.
- May be given with or without food. Be consistent – give the same way every day.
- Mycophenolate mofetil (Cellcept) and Mycophenolate sodium (Myfortic) are different drugs – do not swap.
Mycophenolate

Side Effects
- Stomach cramps, diarrhea
- Nausea, vomiting or heartburn
- Low platelet count
- Low WBC
- Low RBC
- Headaches
- Birth defects to unborn fetus (Need two forms of birth control)

Important Notes
- Given with food helps prevent GI upset
- If patient is experiencing diarrhea, switch drug to Myfortic (enteric coating, less GI irritation)
- REMS education

Sirolimus

![Diagram of T-cell signaling and mTOR inhibition](image-url)
Sirolimus (Rapamune®)

- Antiproliferative agent
- Typically given once a day, however, some individuals may require BID dosing.
- May be given with or without food. Be consistent – give the same way every day.

Side Effects
- Upset stomach, vomiting or diarrhea
- Headaches
- High cholesterol/triglycerides
- Low WBC
- Mouth sores or ulcers
- Low platelets
- Low RBC
- Low platelet count
- Delayed wound healing
- Ance
- Swelling
- Proteinuria
- Leg cramps

Important Notes
- NEVER give grapefruit or juices with grapefruit
- NEVER give fruit related to grapefruit
  > Pomelos
  > Tangelos
**Prednisone**

Antigen presenting cell → B

Signal 1 → TCR

Signal 2 → CD28

Signal 3 → IL2R

Calcineurin → map kinases

mRNA → Cytokines CD25

CD25 → Corticosteroid

Steroids

**Prednisone/Prednisolone**

- Corticosteroid
- Typically given once a day
- Steroid withdrawal protocols

(Deltasone®, Orapred®, Pediapred®)
Prednisone

Side Effects
- Increased blood pressure
- Higher blood sugar
- Upset stomach
- Hunger
- Weight gain
- Edema
- Mood swings, irritability
- Difficulty sleeping
- Headache
- Acne
- Stretch marks

Important Notes
- Long term use may cause weaker bones, slower growth, cataracts

References


