# Side effect of immunosupressants

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ME AGAIN


IT'S ME
AGAIN

**Items of this talk**

**1- Immunosupressants**

**2- Common Side Effects**

**3- Specific side effects**

**4- Others**

# 1- Immunosupressants

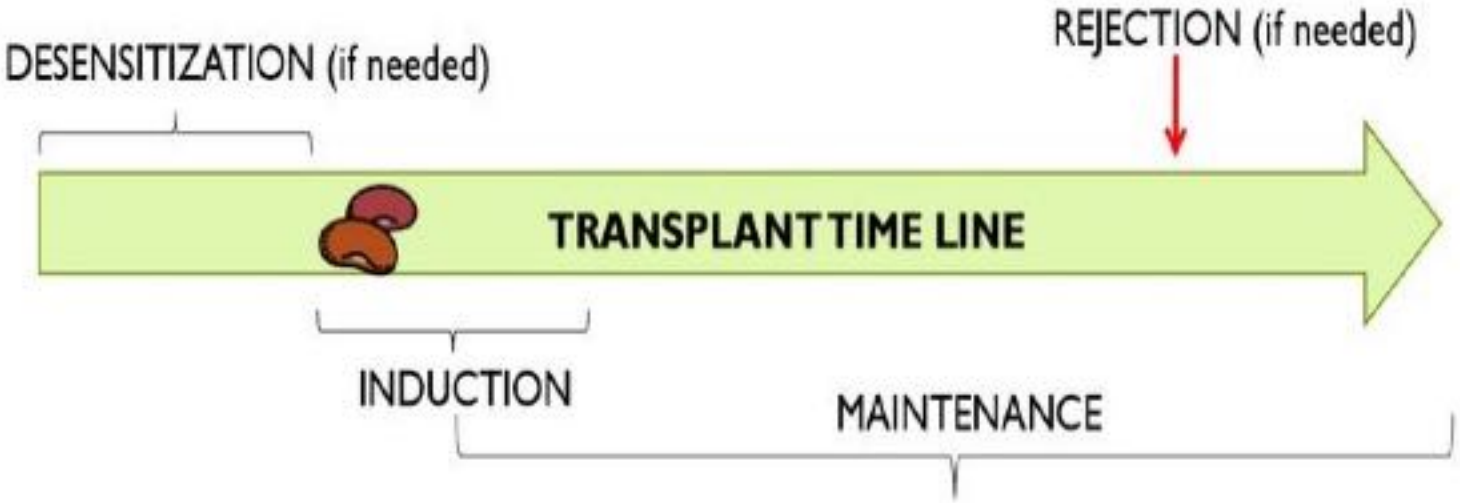
Immunosuppressant's are **drugs or medicines that lower the body's ability to reject a transplanted organ**.

Another term for these drugs is

**anti-rejection** drugs.

# Immunosuppression Types

- Desensitization therapies (aka the "bells and whistles")
- Induction therapies (aka "clearing the field")
- Maintenance therapies (aka "tricking the body")
- Rejection therapies (aka "factory reset")

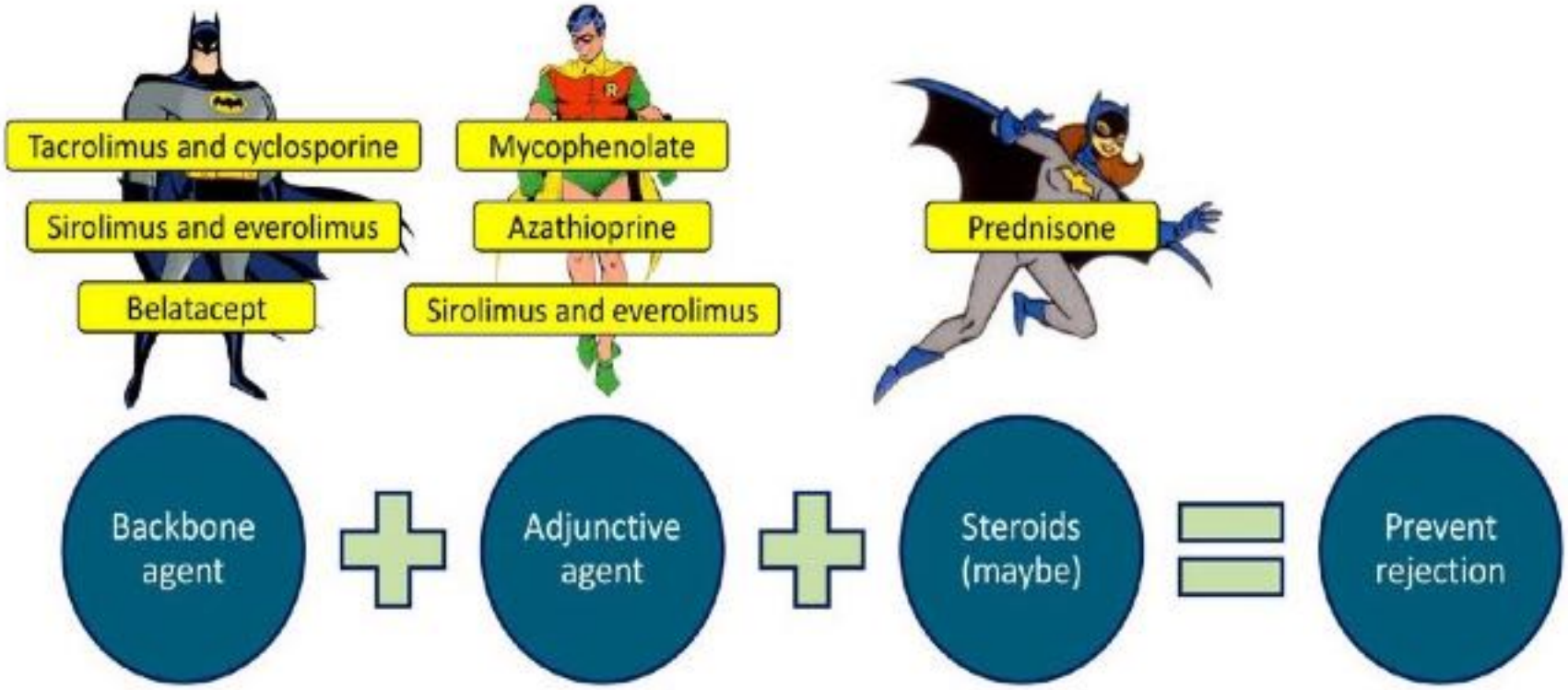


**1- Induction drugs: Powerful antirejection medicine used at the time of transplant**

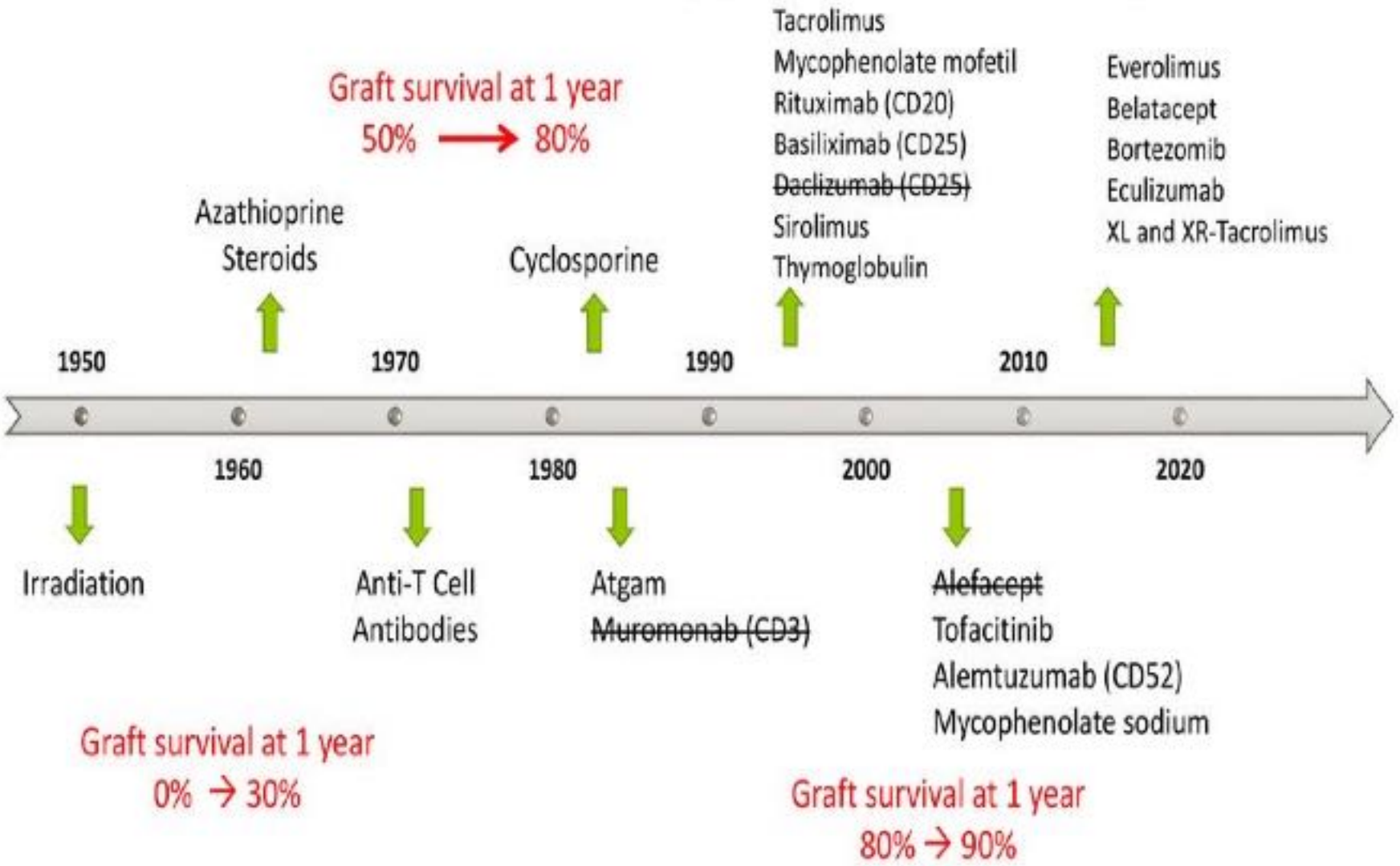
**2- Maintenance drugs: Antirejection medications used for the long term.**

**Think of a real estate mortgage; the down payment is like the induction drug and the monthly payments are like maintenance drugs. If the down payment is good enough you can lower the monthly payments, the same as for immunosuppression**

# Immunosuppression– the Real Heroes!



# Timeline Of Immunosuppression Therapies



# Classification of Immunosuppressant (Based on Mechanism of Action)

## A) Antiprolifirative Agents

1) Drugs Acting on Immunophilins:

a) Selective Inhibitors of Cytokine production )
(Calcineurin Inhibitors) (e.g: Cyclosporine; Tacrolimus)

b) Inhibitor of cytokine function (e.g. Sirolimus).

3) Antimetabolites (Azathioprine; Mycophenolate Mofetil)

4) Alkylating Agents (Cyclophosphamide)

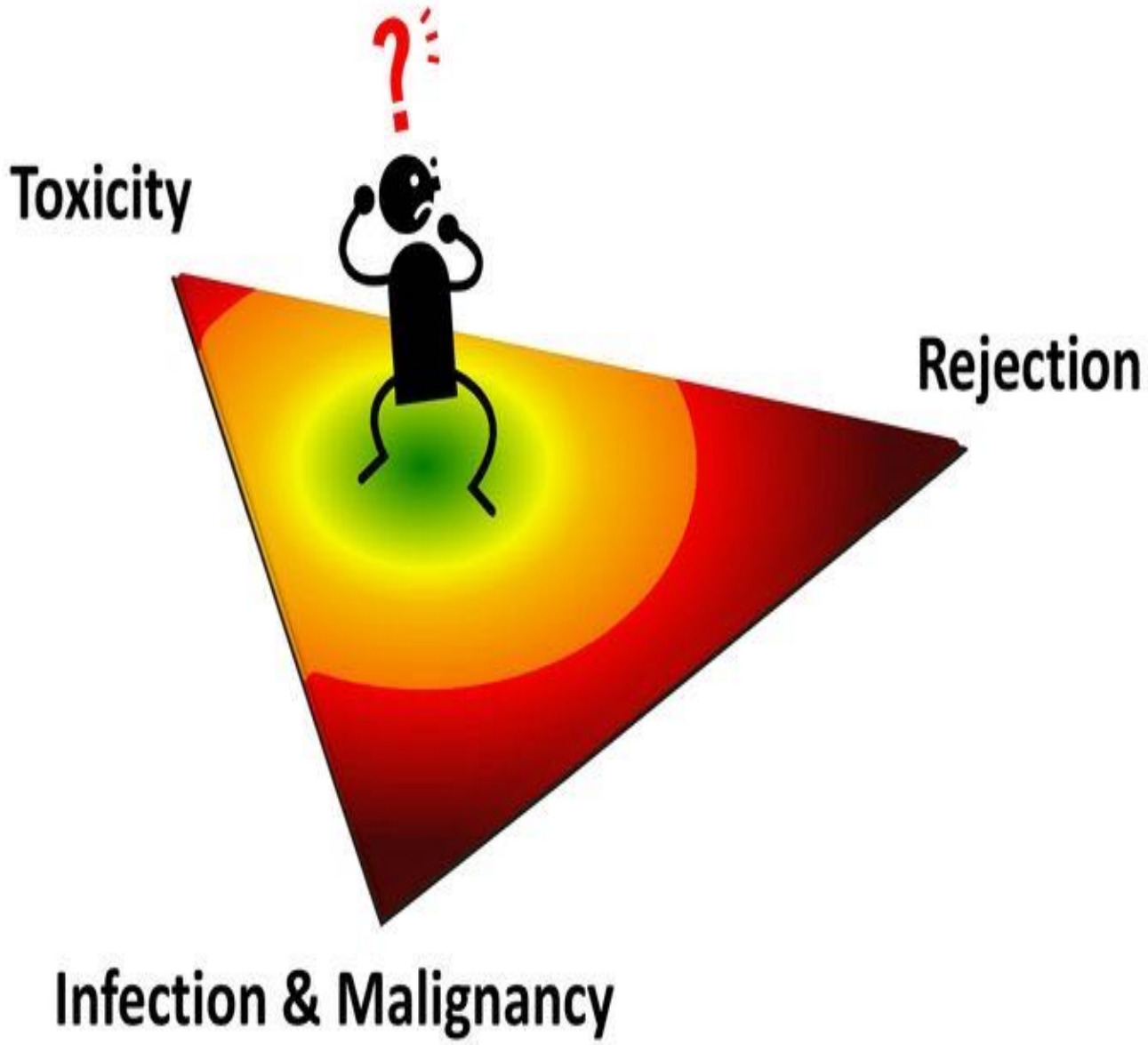
## B) Lymphocyte Depletion Agents

1) Corticosteroids
2. Immunosuppressive Antibodies

a) Polyclonal Antibodies (Antilymphocyte Globulin)

b) Monoclonal Antibodies (Selective inhibitors of IL2 (Basiliximab; Daclizumab)

# Seeking The Perfect Balance



# 2- Common Side Effects

# GENERAL COMPLICATIONS

- INFECTION

CMV infection causing pneumonia,hepatitis

Pneumocystis carnii infection

- NEPHROTOXICITY – Drug dependant
- BONE MARROW TOXICITY
- GIT TOXICITY
- NEUROTOXICITY
- MALIGNANCY

Ten times more potential

Skin cancer & cervix Ca most common

Virus mediated Cancer:Cervix(HPV),Hepatoma (Hep B&C),Lymphoma(EBV).

# Maintenance IMS Toxicities

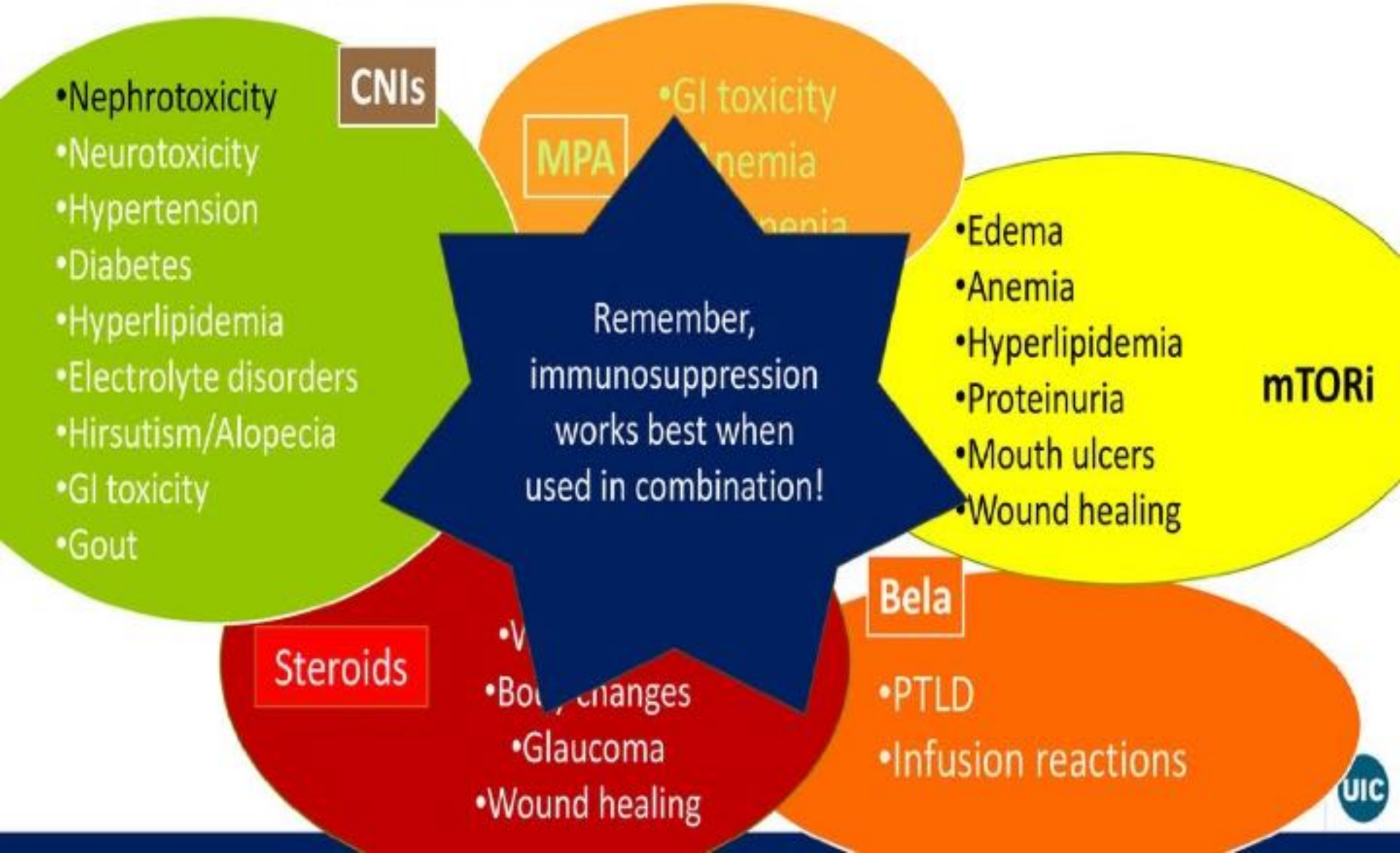


**Table 1.** Distribution of Common Complications of Medication in Renal Recipient After Renal Transplantation[a]

| Variable | Complication | |
|---|---|---|
| | Mild | Severe |
| Excessive hair growth | 86 (45.7) | 56 (29.8) |
| Weight gain | 36 (19.1) | 11 (5.9) |
| Fatigue | 70 (37.2) | 12 (6.4) |
| Tremors | 89 (47.3) | 16 (8.5) |
| Headaches | 23 (12.2) | 7 (3.7) |
| Acne | 39 (20.7) | 2 (2.1) |
| Diarrhea | 57 (30.3) | 10 (5.3) |
| Trouble sleeping | 51 (27.1) | 14 (7.4) |
| Hair loss | 34 (18.1) | 20 (10.6) |
| Gingival overgrowth | 73 (38.3) | 36 (19.1) |
| Increased blood sugar | 95 (50.5) | 24 (12.8) |

[a]Values are expressed as No. (%).

# Type of Immunosuppressive Drugs

| Immunosuppression Category | Common Examples | Nephrotoxicity |
|---|---|---|
| Adrenocorticoids | Prednisolone | No |
| Immunophilin binding drugs | Cyclosporine<br>Tacrolimus<br>Sirolimus<br>Everolimus | Yes |
| Antimetabolites | Azathioprine<br>Leflunomide<br>Methorexate<br>Mycophenolate | No except methotrexate |
| Alkylating agents | Cyclophosphamide | No |
| Biologics | Monoclonal antibodies e.g. Rituximab<br>Poyclonlal antibodies e.g. Thymoglobulin | No |

# 3- Specific Side Effects

# Calcineurin Inhibitors

## 1 CYCLOSPORIN

### Therapeutic Uses:

- **Organ transplantation :**(kidney, liver, heart) either alone or with other immunosuppressive agents (Corticosteroids).
- **Autoimmune disorders :**(low dose 7.5 mg/kg/d). e.g. rheumatoid arthritis, active Crohn's disease, psoriasis, psoriasis, nephrotic syndrome.
- Graft-versus-host disease after stem cell transplants

# CYCLOSPORIN

## Adverse Effects (Dose-dependent)

## Therapeutic monitoring is essential

- Nephrotoxicity

(increased by NSAIDs and aminoglycosides).

- Liver dysfunction.
- Hypertension, hyperkalemia.

(K-sparing diuretics should not be used).

- Hyperglycemia.
- Viral infections (Herpes - cytomegalovirus).
- Lymphoma (Predispose recipients to cancer).
- Hirsutism
- Neurotoxicity (tremor).
- Gum hyperplasia.
- Anaphylaxis after I.V.

# 2 TACROLIMUS

## USES

- Organ and stem cell transplantation
- Prevention of rejection of liver and kidney transplants (with glucocorticoids).
- Atopic dermatitis and psoriasis (topically).

## Toxic effects

- **Nephrotoxicity (more than CsA)**
- **Neurotoxicity (more than CsA)**
- **Hyperglycemia ( require insulin).**
- **GIT disturbances**
- **Hyperkalemia**
- **Hypertension**
- **Anaphylaxis**

**NO hirsutism or gum hyperplasia**

- **Drug interactions as cyclosporine.**

# Clinical Features of Acute CNI Nephrotoxicity

- Elevation of serum creatinine / Reduced glomerular filtration rate
- Occurs early after drug exposure e.g. post-transplant operative period
- Associated with high serum CNI drug levels
- May be associated with electrolyte disturbances e.g. hyperkalemia, metabolic acidosis, hypomagnesemia
- Reversible by lowering dose of CNI or stopping CNI

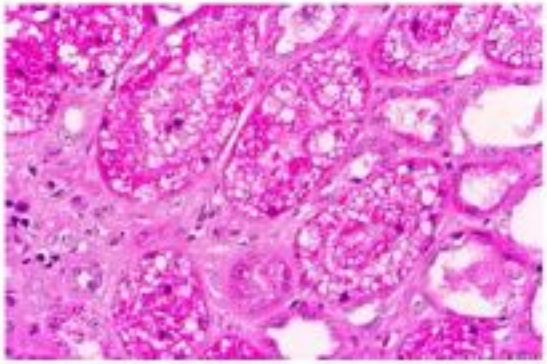
# Clinical Features of Chronic CNI Nephrotoxicity

- Slow, insidious increase in serum creatinine
- Occurs several months after drug exposure
- Associated with hypertension and moderate to nephrotic range proteinuria
- CNI drug levels may be high
- Not reversible – need to reduce dose or discontinue CNI and use alternative immunosuppression

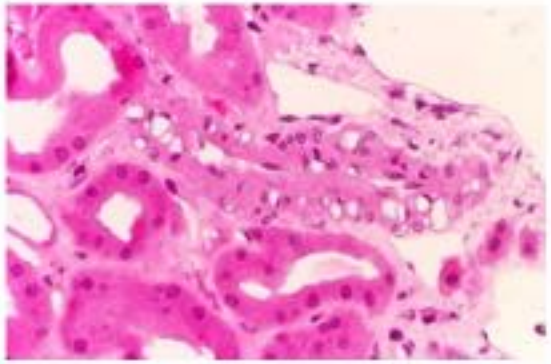
# Risk Factors for CNI Nephrotoxicity

- Systemic exposure - High drug levels
- Older kidney age
- Concurrent use of nonsteroidal anti-inflammatory drugs
- Salt-depletion and diuretic use

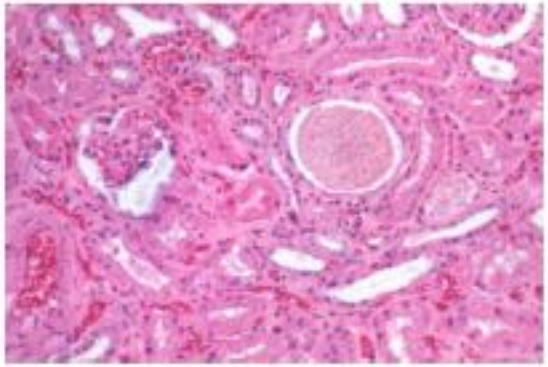
# Pathology of Acute CNI Nephrotoxicity



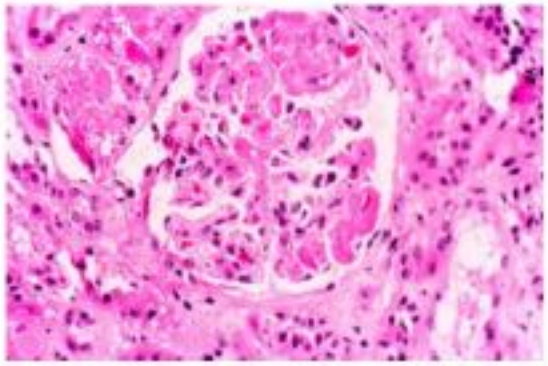
Toxic Tubulopathy
(Isometric tubular vacuolization, Focal tubular calcification)



Acute Arteriolopathy



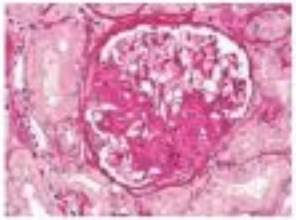
Acute Tubular Necrosis



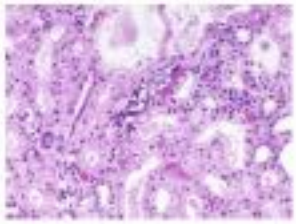
Thrombotic Microangiopathy

# CNI Nephrotoxicity

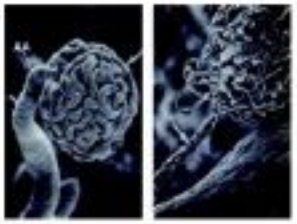
Thrombotic Microangiopathy
Glomerular capsular fibrosis
Global glomerulosclerosis

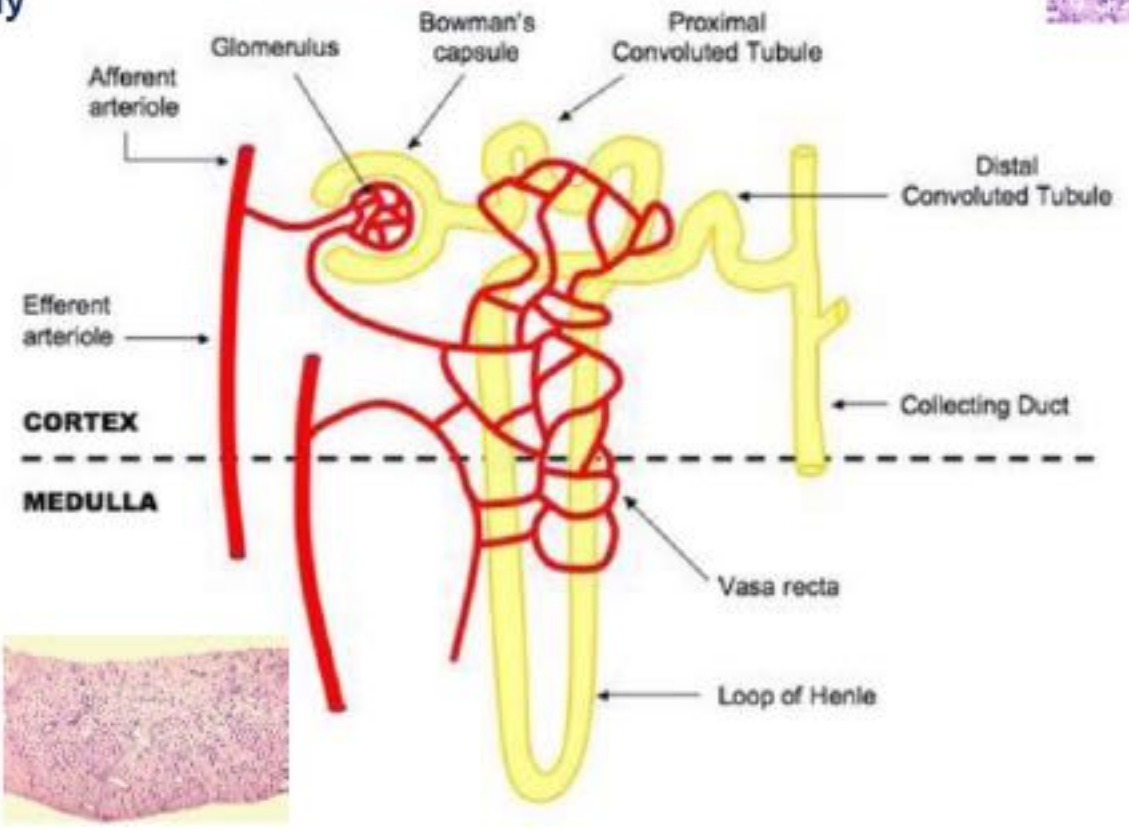


Tubulopathy
Tubular vaculolization
Acute Tubular Necrosis

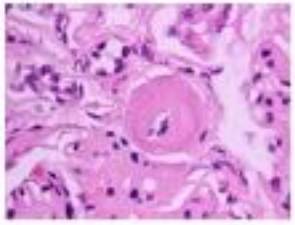


Acute Arteriolopathy






Medial arteriolar hyalinosis



Interstitial Fibrosis (Striped) Tubular Atrophy

# Incidence of CNI Nephrotoxicity

| Indication | Duration of Exposure | Nephrotoxicity |
|---|---|---|
| Kidney pancreas transplant | 1 yr | 30% |
| | 5 yrs | 55% |
| | 10 yrs | 100% |
| Liver transplant | 4 yrs | 16% |
| | 5 yrs | 18% |
| Bone Marrow transplant | 8 yrs | 67% |
| Heart transplant | 5 yrs | 9% |
| | 10 yrs | 9% ESRF |
| Lung transplant | 5 yrs | 14% |
| Intestine transplant | 5 yrs | 21% |
| Autoimmune uveitis | 2 yrs | 21% |

# Prevention and Management of CNI Nephrotoxicity

- Monitor renal function and CNI drug levels regularly
- Avoid other nephrotoxic exposures and drugs that increase drug levels
- Decrease exposure to CNI – avoid, withdraw or minimize (using lower dose)
- Decrease exposure to CNI metabolites – inhibitors of CYP3A e.g. ketoconazole
- Decrease local renal susceptibility to CNI nephrotoxicity – dihyrdopyridine calcium channel blockers, ACE inhibitors and angiotensin II receptor blockers
- Only in animal studies – spironolactone, vasodilatory prostanoids, NO donors, e.g. L-arginine, anti-oxidants, anti-TGF-beta antibodies, statins, supplementation

# Calcineurin inhibitors withdrawal and avoidance

- Increasing evidence indicates that the toxic effects of CNIs contribute to kidney graft loss by cardiovascular death and chronic allograft nephropathy. → two major causes of late graft loss.
- avoiding long-term vascular and renal toxicity.
- Attempts to discontinue CsA have been actively pursued, first by switching to AZA, and later to MMF and sirolimus.

*Oxford clinical nephrology, 3rd edition*

# Table 1. Key drug interactions with calcineurin inhibitors and sirolimus

## Increase levels of cyclosporine, tacrolimus, sirolimus

- Clarithromycin
- Erythromycin
- Azole antifungals
- Diltiazem
- Verapamil
- Isoniazid
- Protease inhibitors
- Grapefruit

## Reduce levels of cyclosporine, tacrolimus, sirolimus

- Rifampin
- Phenytoin
- Carbamazepine
- Phenobarbital
- Nevirapine
- St. John's wort

3

- **Uses of Sirolimus:**
  - 1) can be used together with cyclosporine (to increases the activity of cyclosporine for organ transplanted patients.
  - 2) As replacement of cyclosporine if transplanted patient developed cancer of skin or lips.
  - 3) used in cardiac catheter stint to prevent stenosis??
  - 4) as an ointment for atopic dermatitis and psoriasis
- **Side Effects:**
  - 1) Pneumonitis
  - 2) hyperlipedemia (more then calcineurin-antagonist)

**3) Hypertension**

## Rapamune may interact with

- amphotericin B,
- cimetidine,
- cisapride,
- danazol,
- metoclopramide,
- rifampin,
- rifapentine,
- tacrolimus,
- ACE inhibitors,
- antibiotics,
- antifungal medications,
- calcium channel blockers, or
- HIV medicines.

# 4 AZATHIOPRINE

## Uses

- Acute glomerulonephritis
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Crohn' s disease.

## COMPLICATION

- Bone marrow depression: leukopenia, thrombocytopenia.
- Gastrointestinal toxicity.
- Hepatotoxicity.
- Increased risk of infections.

# Mycophenolate Mofetil (Cellcept®)



The most important discovery among the immunosuppressant agents.

## MOA: (See Figure)

- **Mycophenolic acid acts as non-competitive, selective 7 reversible inhibitor of inosine monophosphate dehydrogenase**
- **Decreases GMP, which is a key enzyme in the de novo pathway of purine synthesis. This leads to suppression of both B and T lymphocyte activation.**
- **PK: Good oral absorption;**

## Side Effects

- **Less than azathioprine, Bone marrow suppresion (leukopenia and anemia); NV and diarrhea (decresed by Enteric-coated form).**
- **Unlike azathiorine it is teratogenic.**

# Alkylating Agents (e.g. Cyclophosphamide)



The most potent immunosuppressant

Destroys proliferating lymphoid cells (cytotoxic agent) also alkylate some resting cells (Thus, it is very toxic)

## Clinical Uses:

- Before the discovery of Mycophenolate, cyclophosphamide was the drug of choice for treatment of many autoimmune diseases like SLE; autoimmune hemolytic diseases and RA.

## Side Effects

- Pancytopenia
- Hemorrhagic cystitis
- Infertility
- Teratogenic

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# Inhibitors of cytokine gene expression - Corticosteroids

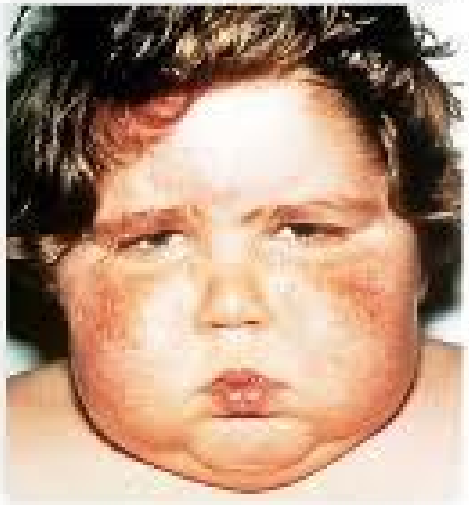
## Indications

- First line therapy for solid organ allografts & haematopoietic stem cell transplantation.
- Autoimmune diseases as refractory rheumatoid arthritis, systemic lupus erythematosus, asthma
- Acute or chronic rejection of solid organ allografts.

# Inhibitors of cytokine gene expression - Corticosteroids

## Adverse Effects

- Adrenal suppression
- Osteoporosis
- Hypercholesterolemia
- Hyperglycemia
- Hypertension
- Cataract
- Infection



# a) Polyclonal Antibodies (Antilymphocyte Globulins)



**Definition: Thymocytes are considered as T-cell precursors.**

What are the differences between polyclonal and monoclonal antibodies?

1) Antithymocyte (**Antilymphocyte) Globulins** (ALG): this antisera can be obtained by immunization of large animals (e.g.rabbits) with human lymphoid cells.

MOA: Antibodies bind to the surface of circulating T lymphocytes forming a comlex. This complex will be phagocytosed in liver or spleen and leading to destruction or inactivation of T cells.

ALG mainly affects the cellular immunity with no effect on humoral, resulting in antibodies against these foreign proteins.

PK: Administered by IM or slow IV infusion with long half-life of 3-9 days

**Side Effects:**

1) Mainly result from the introduction of foreign proteins obtained from heterogeneous serum (Anaphylactic and serum sickness reactions; Local pain and erythema at site of injection).
2) Chills & fever and Leukopenia & thrombocytopenia
3) Viral infections and skin rashes

4) Lymphoma and cancer

## B) Monoclonal Antibodies (Muromonab; Basiliximab; Abciximab; Daclizumab.

9,10

### 1) Muromonab-CD3 (IL-2-antagonist):

From its name, it is murine *monoclonal antibody that prepared by hypridoma technology and directed against the glycoprotien CD3 antigen of human T cells. Used mainly for cases of acute allograft rejections of kidney, heart and liver.*

*it is also used to deplete T cells from donor bone marrow before transplantation.*

*Advantage over ALG: More specific and T lymphocytes return to normal within 24 hr.*

***Side Effects:***

*1) Cytokine release syndrome (Anaphylactoid reactions) Why; and seizure (contraindication)*

*Therefore it is not used.*

# 9 Side Effect of Muromonab

Its use has been declined much because of multiple side effects and the emergence of newer and more selective antibodies therapy

- Anaphylaxis may occur
- *Cytokine release syndrome,* flu-like to dangerous shock-like reactions can occur, & high fever
- CNS: Seizures, encephalopathy, cerebral edema & headache
- Infection like CMV
- Contraindicated with pregnancy, breast feeding, history of seizures, uncompensated heart failure

## 10 · Selective IL-2 Receptor Antagonists

### *Basiliximab* & *Daclizumab*

- ***Basiliximab*** is a chimeric antibody composed of 25% murine & 75% human protein. Block IL
- ***Daclizumab*** is humanized antibody composed of 90% human protein
- Therapeutic Use:
  - Prophylaxis against acute rejection of kidney transplantation
  - Used in combination with steroids or CsA

# Selective IL-2 Receptor Antagonists *Basiliximab* & *Daclizumab* (Contiue..)

- Adverse Effects:

➢ Both are well-tolerated

➢ Gastrointestinal toxicity is the major one

➢ NO antibodies, of clinical relevance, to the drugs are produced

➢ Infection & malignancy are not reported

children and young people should receive pneumocystis prophylaxis with **cotrimoxazole** for 6 months post transplant.

# 11 Cotrimoxazole
## Adverse effects

- Gastrointestinal; N/V, glossitis, stomatitis
- Dermatologic; Skin rash common & severe
- Hematologic; Megaloblastic anemia, leukopenia, thrombocytopenia, hemolytic anemia in pts. deficient in G6PD.
- Drug interactions; Warfarin, phenytoin??, methotrexate??

prophylaxis with **valganciclovir** for at least 3 months post transplant if the **donor** is CMV **positive** and **recipient** CMV **negative** (D+R-)

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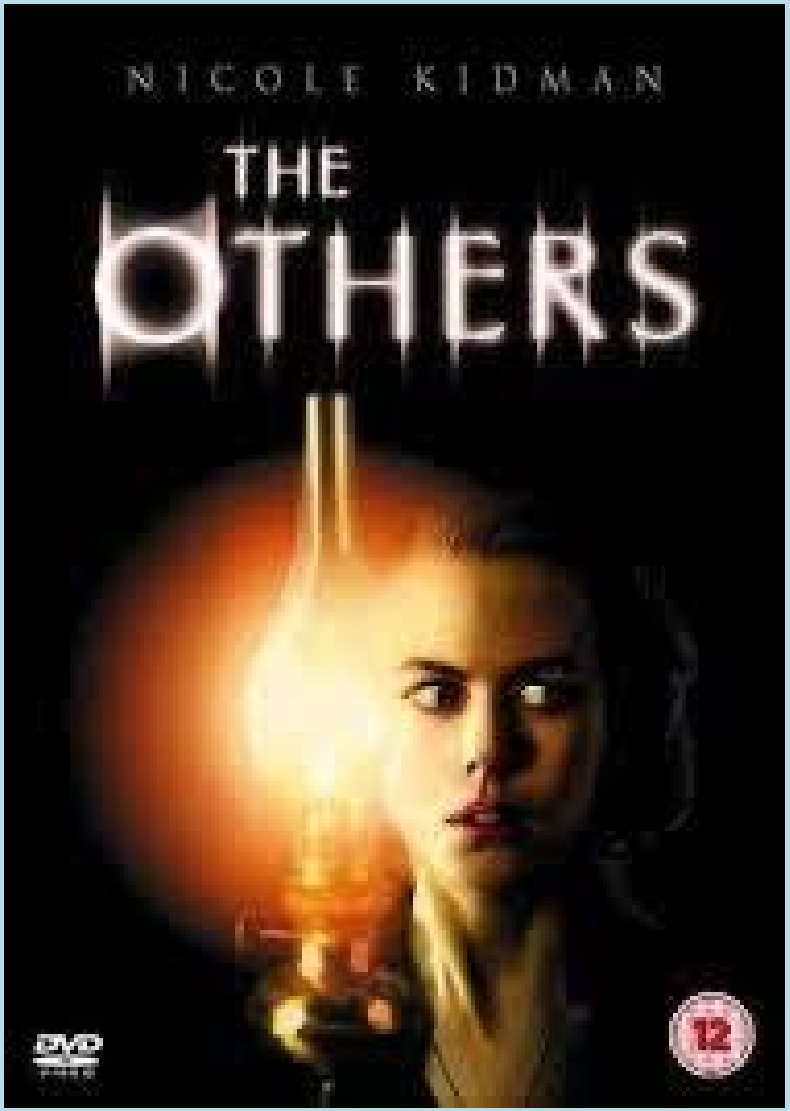
# Valcyte (valganciclovir):

## Side Effects

- Decreased white blood cells (cells that fight infection)
- Decreased platelets (cells that help blood clot)
- Decreased red blood cells
- Kidney damage
- Diarrhea
- Headache
- Nausea and vomiting
- Neuropathy (pins and needle sensation in hands or feet)

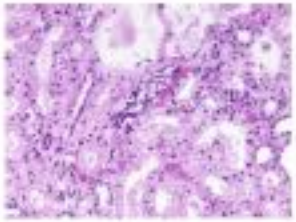
# 4- Others



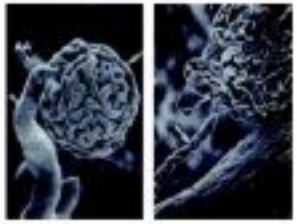
# Drug Nephrotoxicity

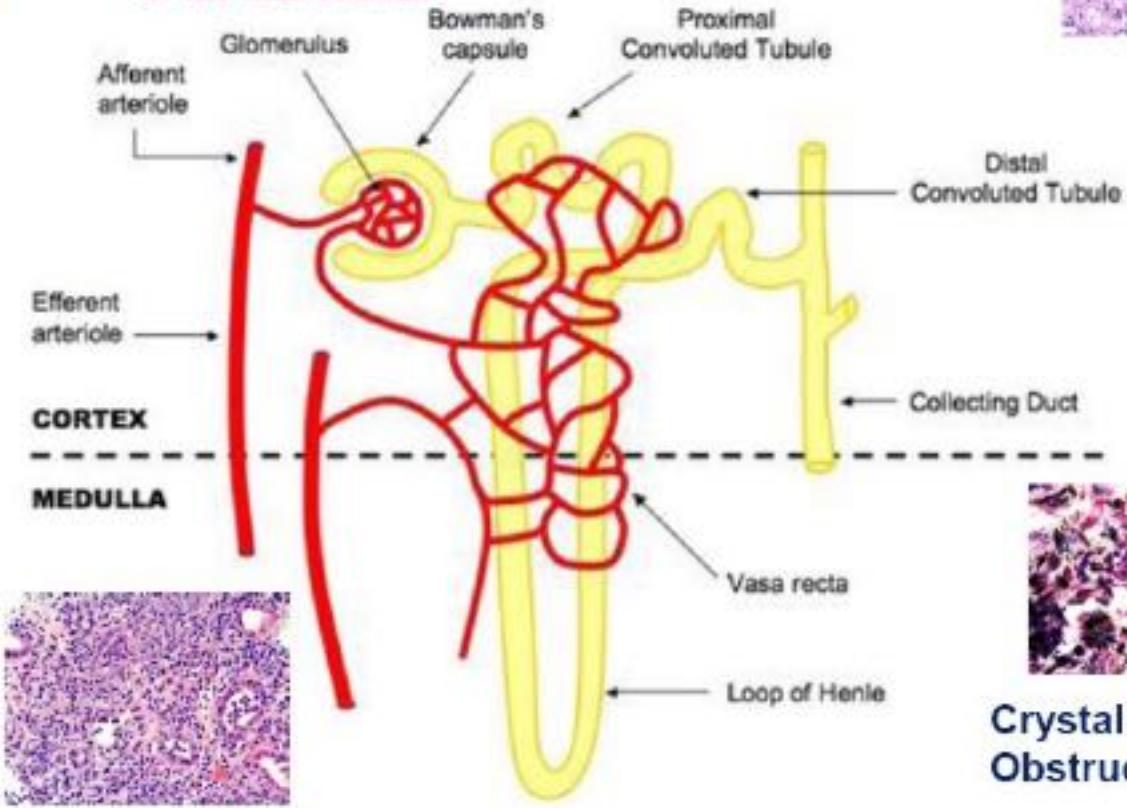
Glomerulopathy
Thrombotic
Microangiopathy

Tubulopathy
Acute Tubular Necrosis
Rhabdomyolysis

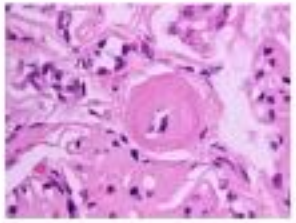


Vasoactive effects






Arteriolosclerosis



Interstitial
Nephritis



Crystal Nephropathy
Obstructive Uropathy

## Table 1. List of chemotherapy agents which cause nephrotoxicity

| | Nephrotoxic mechanism | Associated conditions | Management |
|---|---|---|---|
| Alkylating agents<br>Cyclophosphamide<br>Ifosfamide | Damage to proximal and distal tubules by metabolites oxidative stres | SIADH induced severe hyponatremia, | Hyponatremia management with continuous infusion or bolus hypertonic saline; adequate hydration; AVP ($V_2$) receptor antagonist (tolvaptan); Mesna or N-acetylcysteine electrolyte monitoring; discontinuation |
| Cytotoxic agents<br>Cisplatin<br>Carboplatin | Drug accumul resulting in pr | | Aggressive Short-duration, low-volume hydration; dose adjustment for preexisting renal impairments; magnesium supplementation; mannitol supplementation for preexisting renal impairment and high-dose cisplatin; Forced diuresis; Amifostine radical scavenger; discontinuation; eculizumab for TMA resolution |
| Antimetabolites<br>Methotrexate<br>Pemetrexed<br>Gemcitabine | Vasoconstricti reducing GFR; renal tubules | | Urinary alkylation, hydration, high-flux hemodialysis, carboxypeptidase-G(2) (CPDG2), leucovorin rescue; oral corticosteroids; hyponatremia management with hypertonic saline infusion, fluid restriction, AVP ($V_2$) receptor antagonist (tolvaptan); discontinuation |
| Vinca Alkaloids<br>Vincristine<br>Vinblastine | Neurotoxic eff hypothalamus altered osmot | | Hyponatremia management with continuous infusion or bolus hypertonic saline, fluid restriction, AVP ($V_2$) receptor antagonist (tolvaptan); discontinuation |
| Antitumor antibiotics<br>Doxorubicin<br>Mitomycin C | Induced glom podocyte apo | | Eculizumab for TMA resolution; nephrotic syndrome management through fluid and sodium restriction, oral or IV diuretics, and ACE inhibitors or ARBs |
| Proteasome inhibitors<br>Bortezomib<br>Carfilzomib | Decreased va factor (VEGF) increased ADH kidneys | | Glucocorticoid therapy for management of interstitial nephritis (inconclusive); N-acetyl-l-cysteine upon chemotherapy re-challenge (inconclusive); Hyponatremia management with continuous infusion or bolus hypertonic saline, fluid restriction, AVP ($V_2$) receptor antagonist (tolvaptan); discontinuation |

## Table 1

Antineoplastic agents' nephrotoxicity

| Drug | Incidence rate (%) |
|---|---|
| • Cisplatin | 10–80 |
| • Ifosfamide | 1.4–30 |
| • Methotrexate | 1.8–12 |
| • Nitrosoureas (high dose) | <10 |
| • Carboplatin (high dose) | 0–25 |
| *Rare* | |
| • Actinomycin D | |
| • Anthracyclines | |
| • Cyclophosphamide | |
| • Gemcitabine | |
| • Melphalan | |
| • Vincristine | |

## Table 2

Clinical and laboratory manifestations of ifosfamide-induced nephrotoxicity

| Glomerular toxicity |
| --- |
| • Acute and chronic renal failure, that can result in the suspension of therapy and limit the use of other potentially nephrotoxic drugs. |
| Proximal tubular toxicity |
| • Fanconi's syndrome, which can include: |
| 1. phosphaturia and hypophosphataemia; |
| 2. bicarbonaturia and proximal tubular acidosis; |
| 3. kaliuria and hypokalaemia; |
| 4. calciuria and hypocalcaemia; |
| 5. magnesiuria and hypomagnesaemia. |
| Distal tubular toxicity |
| • Nephrogenic diabetes insipidus |
| • Distal tubular acidosis |

## Table 3

Major risk factors in the onset of ifosfamide-induced renal damage

| |
| --- |
| • Age <5 years |
| • Total dose of drug administered (>60 g $m^{-2}$) |
| • Association with cisplatin |
| • Pre-existing renal damage |
| • Prior nephrectomy |
| • Pre-existing renal malformations |

| Drugs | Common side effects |
|---|---|
| Prednisolone | Weight gain, high blood pressure, gastric irritation, increased appetite, increased risk of diabetes, osteo porosis, cataract |
| Cyclosporine | High blood pressure, mild tremor, excess hair growth, swelling of gum, increased risk of diabetes, kidney damage |
| Azathioprine. | Bone marrow suppression, increased risk of infection |
| MMF | Abdominal pain, nausea, vomiting and diarrhea |
| Tacrolimus | High blood pressure, diabetes, tremor, headache, kidney damage |
| Sirolimus/ everolimus | High blood pressure, low blood cell count, diarrhea, acne, joint pain, increased cholesterol, triglycerides |

## 5. IMMUNOSUPPRESSION GUIDELINES

***The goal remains to maintain optimum level of immunosuppression***
*(i.e. minimize acute rejection (AR) and not to increase incidence of infection and malignancy)*
**with minimal toxicity.**

**We recommend that immunosuppressive therapy i**
**immunological risk and concerns with individual age**

Immunological risk stratification:

***Immunological low risk:***
- 1st time transplant recipients who have less than
luminex)
- Repeat transplant recipients who have not agg
transplant (i.e. not within the first year) & who have le

***Immunological intermediate risk:***
- Transplant recipients with PRA between 20%* & 80%
- Rh incompatibility
- Repeated blood transfusions
- Previous (NOT current), not otherwise ex
(lymphocytotoxicity)/ DSA with the same donor

***Immunological high risk:***
- Transplant recipients who have rejected one or more
the 1st year posttransplantation)
- Any recipients with greater than 80% PRA.
- Transplant following any desensitization procedure

** PRA >0% and <20% is sometimes considered intermed*

**We recommend that antibody induction therapy be**
**transplant recipients.** The first dose should be g
declamping

IL2 receptor antibody (Basiliximab) is suggested for pa
risk; in a dose of

*- 20 mg x 2 doses on day 0 and day 3-4 in recipients weigh*
*- 20 mg in 1-2 divided doses in recipients weighing < 35kg*

**T cell depleting therapy (ATG; 5-8mg/Kg or thymog**
**recommended for induction in high immunological**
**recommended in patients with increased risk of inf**

**Maintenance**
**cyclosporine)**
**in most transp**

In low risk transp
elimination with

Azathioprine is g
used in individua

**We recommend**
**KTRs**

***Suggested use of***

Methylprednisolone
-The night be
-At the time o

- The same dose is
converted to oral wh
mg/m2 by day 14

- After the first month
Further management
AR

***Suggested use of C***

-May be started before

-Be aware of food and drug interactions

-Tacrolimus is preferentially suggested in patients with dyslipidemia, significant hirsutism & in those who are considered immunological high risk

**-Tacrolimus:** is started in a dose of 0.15mg/kg/day in 2 divided doses

**-Cyclosporine**: is started in a dose of 8-10 mg/kg/day (250mg/m2/day) in 2-3 divided doses (3 in younger children)

-Both are adjusted to therapeutic ranges based on drug level monitoring

-The suggested target trough level of Tacrolimus is 10-15 ng/mL in the first month and 5-10 ng/mL later (higher in the first 3-6 months)

-The suggested target trough level of Cyclosporine is 200-250 ng/mL in the first month, around 150 ng/mL up to 6 months and around 100 ng/mL thereafter

***Suggested use of Mycophenolate:***

Mycophenolate mofetil (MMF) or Mycophenolate sodium (MPS) may be used. Patients differ in tolerance

-Starting dose of MMF is 1200mg/m2 in 2 divided doses, starting 2 days preoperative
-Lower doses 900mg/m2 may be used with Tacrolimus
-Higher doses up to 1800mg/m2 may be used when needed (immunologically) & tolerated (hematologically & GIT)

The starting dose of MPS is 900mg/m2 in 2 divided doses

Mycophenolate should be separated from Tacrolimus or Cyclosporine by 2hrs

***Target of rapamycin inhibitors***

-mTORi (sirolimus or everolimus) based protocols may be used in low immunological risk patients

-The loading dose of sirolimus is 3mg/m2 once followed by a maintenance of 1mg/m2 once daily in patients <40Kg. Adults/ larger patients receive 6mg loading and 2mg/day maintenance. Doses are adjusted to a target trough level of 5-15ng/mL

-The starting dose of everolimus is 0.8mg/m2/dose twice daily and target trough level is 3-8ng/mL

-They are not recommended in the first month

-They have advantages regarding lower risk with malignancy and certain infections as CMV

-They may cause/ increase proteinuria and dyslipidemia in a dose-dependent manner

-Everolimus allows reduction in CNI dose (60% with CsA and 40% with tacrolimus)


THANK YOU!

**1- Acute CNI nephrotoxicity is**

**A- irreversible**

**B- reversible**

**C- only tubular**

**D- not related to drug level**

**2- Hemorrhagic cystitis occurs as a side effect of**

**A- Steroid**

**B- CNI**

**C- Cyclophosphamide**

**D- All of the above**

**3- allergic reactions are liable to occur with**

**A- ALG**

**B- Sirolimus**

**C- CNI**

**D- Azathioprine**