



Government of **Western Australia**  
North Metropolitan Health Service  
Sir Charles Gairdner Osborne Park Health Care Group

# Transplant Medication



Living With Your Transplant:  
*Transplant Medications*



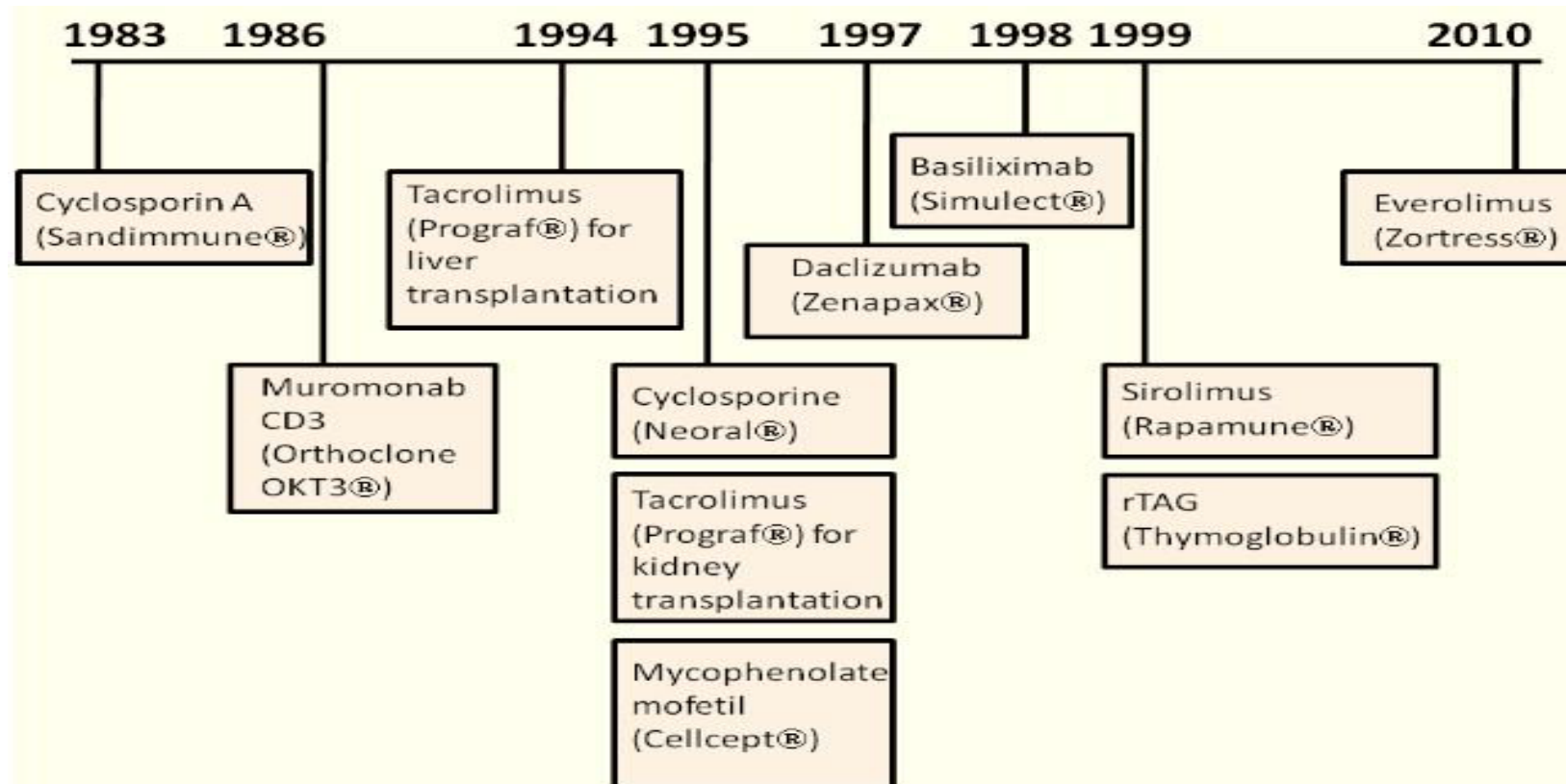
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# Classes of Medications used

- Medicine to keep your body from attacking or rejecting new organ
- Medicine that protects m infection.
- Medicine to prevent or control side effects



# Timeline-Discovery of Immunosuppressants

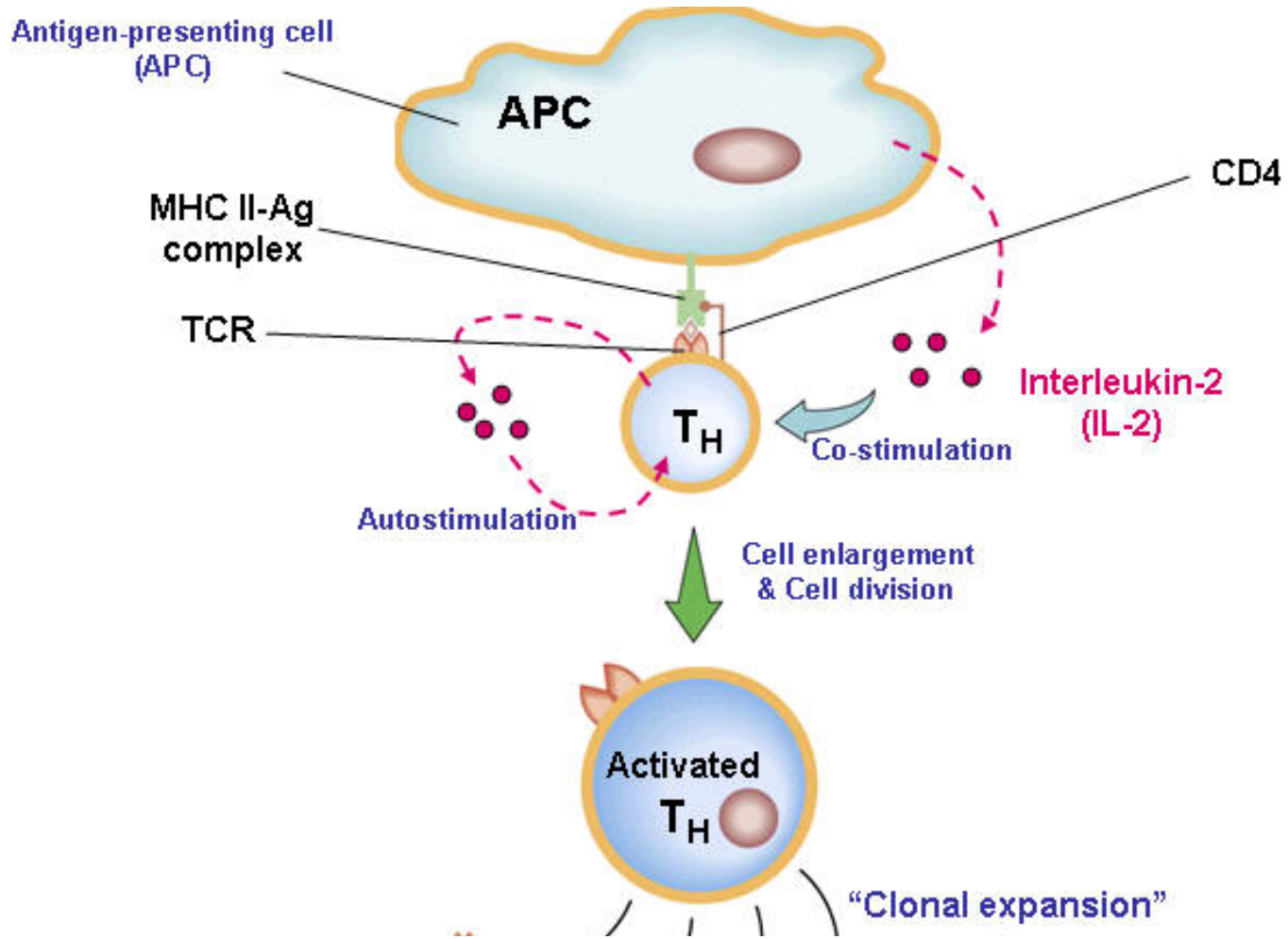


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# The Immune System

- Immune system distinguishes self from non self
- Network of cells, tissues and organs that work together to protect the body against foreign invaders or objects
- Protects by attacking and destroying any foreign objects found in the body
- Foreign object can be bacteria ,virus or transplanted organ
- Immune system recognises transplant as a foreign object and tries to destroy it
- Two types of immune response- T cells and B cells





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# Goals of Transplant Therapy

- Reduce the amount of immunosuppression
- Decrease side effects
- Decrease toxicity and long term effects
- Enhance long term patient and graft survival
- Provide reasonable cost effective therapy
- Improve patient adherence and quality of life



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# Immunosuppressive Strategies

- 1. Induction-prior to transplant
- 2. Acute phase-First month post transplant
- 3. Maintenance-long term treatment
  
- Treatment of rejection



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# Rejection

- **Types of rejection**
- **Hyperacute**-immediately post transplant
- **Acute**
  - Treatment with high dose methylprednisolone
  - If process not reversed thymoglobulin (anti thymocyte globulin, ATG) can be used





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# Chronic Rejection

- Most common cause of late transplant failure
- Gradual unrelenting decline in graft function
- Characteristic histopathological findings-biopsy
- Occurs over months or years
- Low grade immune mediated injury similar to acute type
- No specific therapy to reverse process
- Return of original disease also a common cause of graft loss



# Immunosuppressant Regimen

- More than one agent used so that the dosage of each agent can be reduced
- Avoids or reduces drug specific toxicity
- Maintains adequate control of immunosuppression
- Different combinations used
- Generally one from each group
  - 1. Corticosteroid-methylprednisolone (IV) prednisolone (oral)
  - 2. Calcineurin inhibitor-ciclosporin, tacrolimus
  - 3. Antimetabolites-mycophenolate, azathioprine
  - 4. Basiliximab/thymoglobulin (Kidney .transplant)
  - +/- mTOR inhibitors-sirolimus, everolimus



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# Induction

- Activation of patients immune system strongest early after engraftment
- Recipients immune system requires suppression to avoid rejection
- High dose intravenous methylprednisolone
- Oral loading with immunosuppressive drugs
- Cyclosporin/tacrolimus, mycophenolate



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# Maintenance

- Prevent or minimise problems associated with long term transplantation
- Inability to determine exact dosage required to prevent rejection and avoid over immunosuppression
- Significant side effects of immunosuppressive drugs
- Balance between lowest possible dose (avoidance of side effects ) and dose required to prevent rejection



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# Complications of Immunosuppression

- Risk of infection
- Increased risk of cancer particularly skin cancer and lymphoma
- Increased risk of vascular disease
- Viral infection-proliferation of Epstein Barr virus predisposes to lymphoproliferative diseases
- Lymphoproliferative diseases cause significant morbidity/mortality
- Invasive fungal infections can also occur



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# Calcineurin Inhibitors

- Ciclosporin and Tacrolimus
- Dosed twice daily as close to as possible to 12 hours apart
- Ciclosporin levels taken at 2 hours post dose
- Tacrolimus level just prior to next dose
- Form a complex with immunophilin.
- Drug-immunophilin complex blocks action of calcineurin activated T cells
- Stimulation of B and T cell proliferation blocked



# Side Effects- Calcineurin inhibitors

## Ciclosporin

- Nausea & vomiting- tendency to GI bleeds
- Hirsutism-Does not respond well to dose reduction
- Gingival hypertrophy-dental hygiene
- Neurotoxicity-particularly tremor (50%)
- Hypertension
- Hypomagnesemia
- Hyperkalaemia
- Gout-increased uric acid levels
- Hepatotoxicity-responds to dose reduction

## Tacrolimus

- Binds to FK binding protein which inhibits calcineurin activity
- Monitoring of trough levels
- Twice daily on empty stomach
- Similar side effect profile to cyclosporin
- Most common headache, tremor, nausea hypertension,diarrhoea,renal dysfunction
- Higher incidence of hyperglycaemia
- Unlike cyclosporin can be used to treat rejection





## Mycophenolate mofetil/sodium



- Often started prior to transplant if living donor
- Used in combination with tacrolimus/cyclosporin and steroids
- Two forms-mycophenolate sodium /mycophenolate mofetil
- Major side effect gastrointestinal disturbances particularly diarrhoea
- Mycophenolate Sodium enteric coated-may cause less GI effects
- Avoid taking with antacids





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# Corticosteroids

- Prednisolone
- Used for induction, maintenance and rejection (methylprednisolone)
- Varying doses dependent on organ transplanted
- Can cause increase in blood sugar level
- **Some side effects dose related and reversible**
- eg. Cushingoid appearance,
- psychiatric disturbances and myopathy uncommon at doses < 30mg day
- Complications such as thin skin osteoporosis and cataracts related to long term therapy even at low doses
- Avoid rapid withdrawal-Myalgia & arthralgia

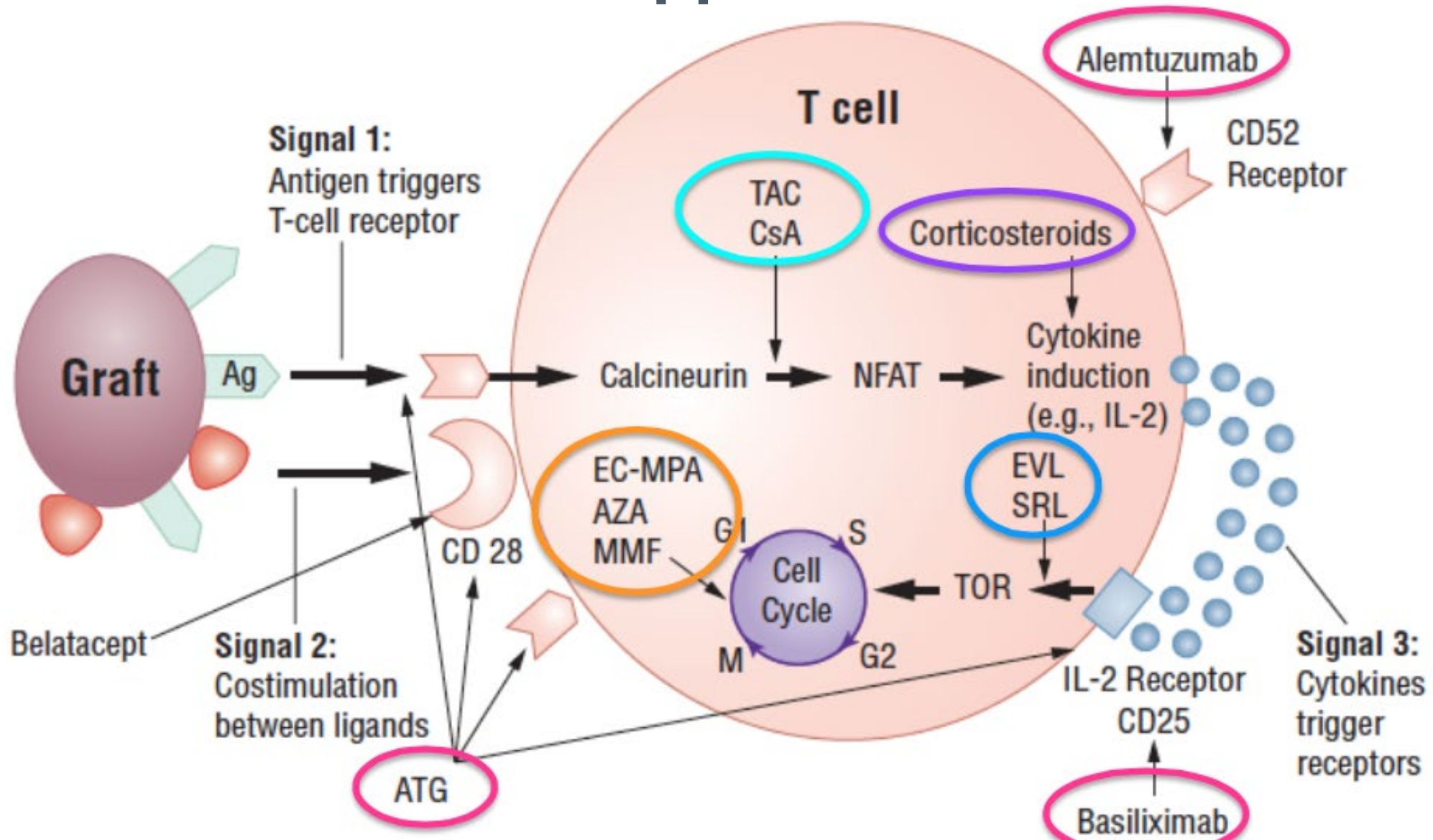


# mTOR inhibitors-Everolimus and Sirolimus

- Alternate immunosuppressants to calcineurin inhibitors (tacrolimus & ciclosporin)
- Sirolimus once daily dosing everolimus twice daily dosing
- Most significant side effects hypercholesterolaemia, hypertension, rash, hypertriglyceridaemia, thrombocytopenia, interstitial pneumonitis, impaired wound healing, arthralgia, stomatitis, dyspnoea ,cough
- Role in patients with diminished renal function from cyclosporin or tacrolimus
- Sirolimus may have a role in reducing incidence of skin cancer I
- Not usually as well tolerated as CNI's



# Sites of Immunosuppression



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# Treatment of Rejection

- First option high dose methylprednisolone eg 500mg for 3 days
- Varying doses depending on organ and physician preference
- If rejection not resolved ;
- Rabbit antihymocyte globulin Thymoglobulin<sup>®</sup>
- Dosed for 7-10days.
- Premedication given prior to treatment
- Increasing dose of tacrolimus can also reverse rejection



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# Timeline of infections after solid organ transplantation

Fishman. DOI: 10.1056/NEJMra064928



<1 mo

Pre-existing infections;  
Nosocomial, technical complications

- Antimicrobial-resistant spp:** MRSA, VRE, *Candida* (non-*albicans*)
- Hospital acquired infections:**
  - Catheter infection
  - Wound infection
  - Anastamotic leaks, ischemia
  - C.diff*
- Donor derived** (uncommon): HSV, LCMV, rabies, WNV, HIV, *T.cruzi*
- Recipient-derived** (colonization): *Aspergillus*, *Pseudomonas*



1-6 mo

Maximal immunosuppression:  
Opportunistic infections, activation of latent infections

- If PJP and antiviral (CMV, HBV) ppx:**
  - BK polyomavirus nephropathy
  - C.diff* colitis
  - HCV, Adenovirus, influenza
  - Cryptococcus neoformans*
  - M.tuberculosis*
- Without ppx:**
  - PJP, HBV
  - Herpes viruses (HSV, VZV, CMV, EBV)
  - Listeria*, *Nocardia*
  - Toxoplasma*, *Strongyloides*, *Leishmania*, *T.cruzi*



>6-12 mo

Stabilized and reduced IS:  
Community-acquired

- Community-acquired** pneumonia, UTI
- Aspergillus*, atypical molds, *Mucor* spp
- Nocardia*, *Rhodococcus* spp
- Late viral:
  - CMV (colitis/retinitis), HBV, HCV
  - HSV encephalitis
- Community acquired (SARS, WNV)
- JC polyomavirus (PML)
- Skin cancer, lymphoma (PTLD)



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# Prevention of infection

- **Pneumocystis jirovecii pneumonia PJP**
- Sulphamethoxazole/trimethoprim- Resprim<sup>®</sup> Septin<sup>®</sup> Bactrim<sup>®</sup>
- Commonly used three times a week although other regimens used.
- Treatment time varies may continue while on immunosuppressive therapy
- Usually well tolerated.
- Cannot use if sulphur allergy
- Alternative therapies- pentamidine, dapsone



# Prevention of infection cont.

- **Viral Prophylaxis**
- Cytomegalovirus (CMV)
- Valganciclovir 450mg-Usual dose 900mg/day
- Reduced dose if kidney function not normal
- 60-80% infection rate in community
- No symptoms in immunocompetent patients
- Can be reactivated or donor may carry infection
- In transplants prevention in the early transplant period
- Dosed for 3-6 months





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# Prevention of infection

- **Fungal Prophylaxis**
- Prevention of *Candida albicans*-thrush
- Nystatin liquid- 1ml four times a day
- Swirled around mouth and swallowed after meals and at bedtime
- Other antifungals may be used
- Fluconazole –*candida* (interacts with tacrolimus)
- Voriconazole-, *Aspergillosis*, *cryptococcus*(interacts with tacrolimus)
- Amphotericin



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# Infection precautions for transplant patients

- Increased risk of infection due to lifelong immunosuppression.
- 1. Handwashing:** Regular handwashing is crucial. Use soap and water or an alcohol-based hand sanitizer.
- 2. Animal Safety:** Avoid changing cat litter boxes and minimize contact with pets.
- 3. Food and Water Safety:** Ensure food is well-cooked and avoid raw seafood and unpasteurized cheeses.
- 4. Avoid Sick Individuals:** Steer clear of exposure to sick people, especially those with respiratory viruses.
- 5. Family Vaccinations:** Ensure family members are up-to-date on vaccines, such as flu shots.



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# Cancer Risk in Transplant Patients

- Transplant recipients have an increased risk of developing new cancers in general (1-2% per year) and a 15-20 % higher incidence of certain types of cancer.
- Skin cancer and lymphomas are the most common types of cancer seen post transplantation. Increased rates of SCC and melanoma
- Increased risk of cervical, breast cancer and colorectal
  
- **Influenced By:**
  - Sun exposure
  - Type, extent, and duration of immunosuppression
  - Concomitant viral infection.



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# Treatment Options for Skin Cancers

- Acitretin – Evidence that secondary reduction BCC's and SCC's  
Side effects can limit tolerability
- Nicotinamide -Vitamin B3 500mg twice day has been shown in some studies to be useful in reducing skin cancers in solid organ transplants
- Sirolimus-Siroskin®
- Trial in Eastern Australia examining use of sirolimus cream to prevent skin cancers on head and neck



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# Preventative Measures

- Careful screening of the patient and donor prior to transplantation to help detect an underlying preexisting malignancy.
- Avoidance of excess immunosuppression, especially with calcineurin inhibitors (CNIs), or repeated exposure to agents that selectively target T lymphocytes such as antithymocyte globulin (ATG) .
- Sun-protective measures, such as sun avoidance and regular use of sunscreens and sun-protective clothing



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# What supplements or herbal products to avoid after receiving a transplant

- Vitamin C
- St. John's Wort
- Herbal teas: green tea, chamomile, peppermint, dandelion
- Echinacea
- Ginseng
- Feverfew
- Liquorice (cyclosporin)



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# Foods to avoid post transplant

- **The below fruits and juices may interact with your immunosuppression, causing toxicity. They should be avoided.**
- Grapefruit and grapefruit juice (please note that some citrus-flavored drinks have a grapefruit extract in them, so it is important to check ingredient lists.)
- Pomegranate and pomegranate juice
- Seville Oranges (normal oranges are fine in moderation)
- Other fruits and vegetables that should be consumed in moderation are grapes, cranberries, tangerines, cauliflower, and broccoli.<sup>1</sup>



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# Drug Interactions

- Cyclosporin, tacrolimus, sirolimus and everolimus all metabolised by the same liver enzyme (CYP450 3A4)
- **Inhibition** of this enzyme will cause increased levels
- Responsible for metabolism of > 30% of drugs
- Azole antifungals-fluconazole, ketoconazole
- macrolide antibiotics-erythromycin
- calcium channel antagonists-diltiazem, nifedipine
- **Induction**- Decreased levels
- Rifampicin, phenytoin, carbamazepin, St Johns Wort





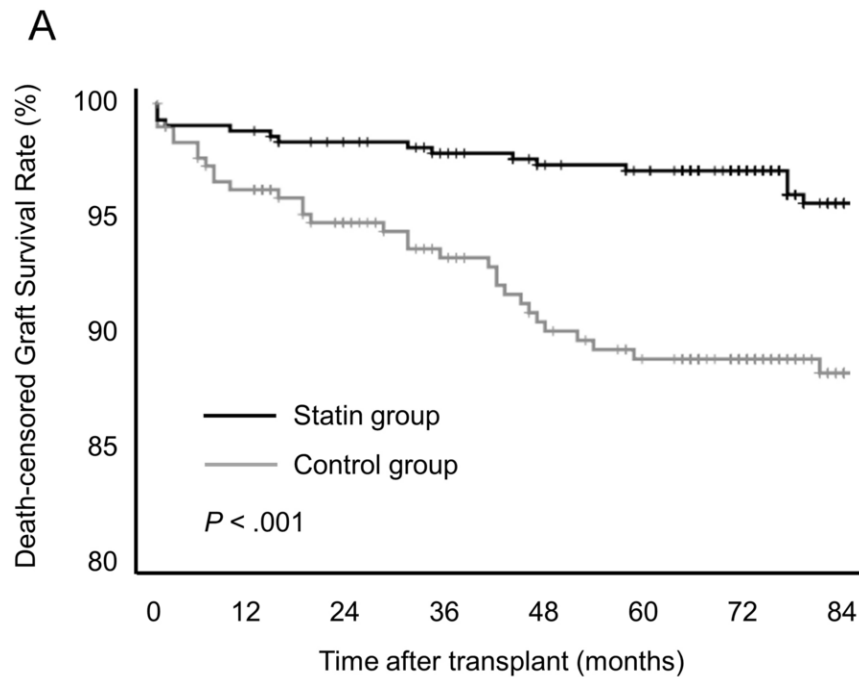
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# “Statins”

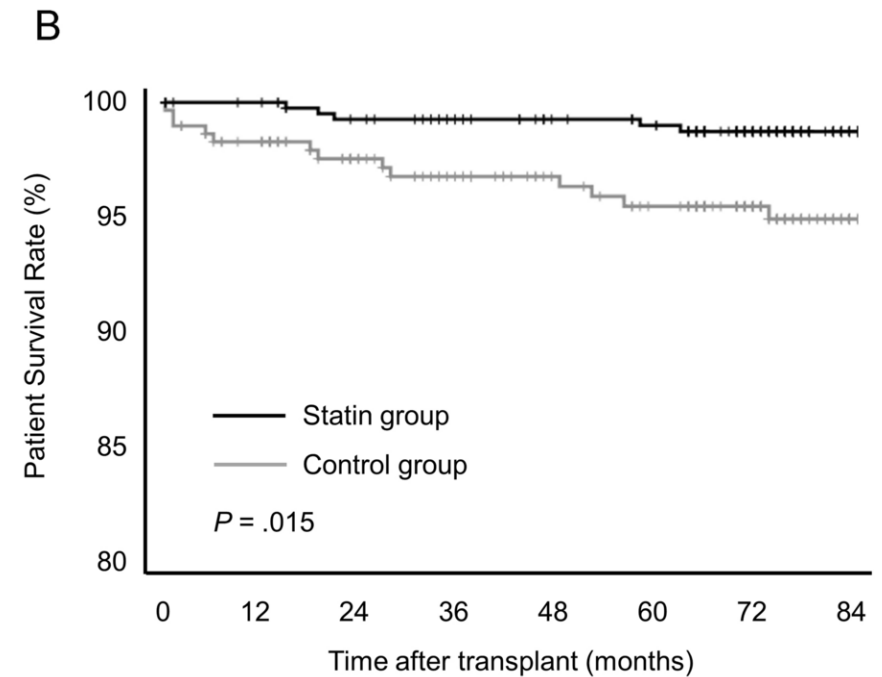
- Hyperlipidaemia common in transplant patients and is exacerbated by immunosuppressive therapy and results in significant cardiovascular morbidity and mortality
- Interaction of statins with some of the immunosuppressants
- Most interactions with cyclosporin (Can use pravastatin rosuvastin)
- Important to report potential symptoms of toxicity, such as myalgias, weakness, fatigue, and nausea.
- Tacrolimus less likely to interact with statins.



# Statins



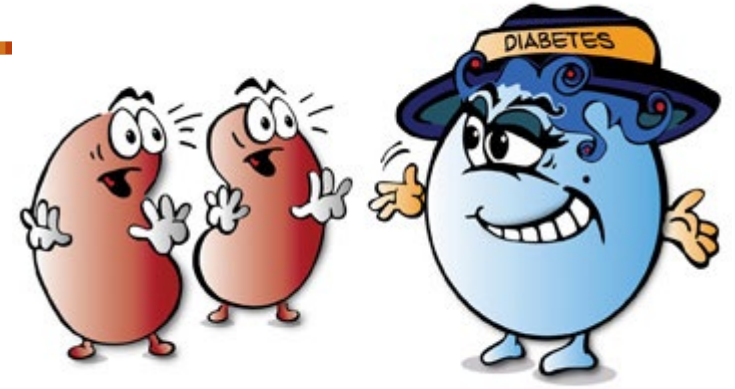
No. at risk		0	12	24	36	48	60	72	84
Control		300	280	256	241	226	217	192	137
Statin		414	413	404	394	381	375	332	237



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# Increased blood sugar levels



- Drugs used in immunosuppression can increase blood sugar levels
- Steroids and tacrolimus have increased blood sugar levels as a side effect
- If already using insulin doses may have to be increased
- Linagliptin oral antidiabetic drug may be added
- As doses of steroid decreases blood sugar levels may improve





## Medication Profile

Pharmacy Department  
 Sir Charles Gairdner Hospital  
 Verdun Street, Nedlands  
 PERTH WA 6009  
 Telephone 08 6457 2334


Name:

20 March, 2024

*You have been prescribed the following medication. This information will help you use it safely and effectively.*

Medication Name	Other Names	Number to Take				Purpose for Medication	Special Instructions
		Morn- ing	Mid- day	Even- ing	Bed- time		
Tacrolimus 500microgram, 1mg ,5mg	<b>Prograf</b> <i>Use this brand only</i>	mg		mg		To suppress the immune system/prevent organ rejection	Take at same time each day . Delay dose till after blood test taken on clinic days. 500microgram 1mg 5mg
Mycophenolate Sodium 360mg	Myfortic	2		2		To suppress the immune system/prevent organ rejection.	Take with food. If rash, fever, stomach upset or vomiting occur see your doctor straight away. 
Prednisolone tablets 5mg,25mg	Panafcortelone Solone	Take 30mg each morning (1x5mg tablet and 1x25mg tablet)				To suppress the immune system/prevent organ rejection.	Take after food to avoid stomach irritation, strictly as directed 5mg 25mg <b>Note: total dose on discharge 30mg. Will decrease with time</b>
Sulfamethoxazole and trimethoprim 800/160mg	Septtrin Forte Bactrim DS Resprim Forte	Take One tablet in the morning on Monday, Wednesday and Friday				To prevent pneumonia	Take with food to avoid stomach irritation. R F 160 800
Nystatin Mixture 100000u/mL	Nilstat Mycostatin	1ml	1ml	1ml	1ml	To prevent fungal infection	Drop onto the tongue and swirl around mouth for a few minutes before swallowing after meals and at bedtime.
Pantoprazole Tablets 40mg		1				Prevent stomach discomfort	Swallow whole, do not chew or crush. P 40



Medication Name	Other Names	Number to Take				Purpose for Medication	Special Instructions
		Morn- ing	Mid- day	Even- ing	Bed- time		
Valganciclovir Tablets 450mg	Valcyte	Take 1 tablet twice each week on Mondays and Thursdays				Prevent viral infection	Swallow whole with food. Variable dose dependent on renal function. <b>Dose will increase as kidney function improves.</b> 
Calcium Carbonate/ colecalciferol tablets 600mg	Calci-600	1				Calcium and vitamin D supplement	
Paracetamol Tablets 500mg		2	2	2	2	Pain Control	<b>Take regularly for the next week, and then when required thereafter.</b> Do not take more than 8 tablets (4g) of paracetamol in 24 hours.

- Remove medication from package only for immediate use, - Do not change treatment unless directed by your doctor,
- Do not give your medication to other people or use it for other illnesses, - Try to have all your prescriptions dispensed at the same Pharmacy
- Do not run out of medication.

If you need further assistance call the 'phone number at the top of this profile.

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# Costs of Medication

- Most medication covered by PBS (Pharmaceutical Benefits scheme)
- Costs-Concession card holders-\$7.70 per prescription  
General patients -\$31.60 per prescription
- Once threshold is reached -\$277.20 for concession  
-\$1647.90 for general
- Eligible for PBS Safety net card
- Costs becomes free for concession card holders and \$7.70 for general patients

