2021

MEDICATION GUIDELINES FOR SOLID ORGAN TRANSPLANTS

BC TRANSPLANT
Provincial Health Services Authority

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- *Tacrolimus target level update*
- *Hep B section update*
- *Management guidelines section*

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Introduction

Patients who undergo solid organ transplant require lifelong immunosuppression to prevent organ rejection. In organ transplantation, the ideal form of immunosuppression is to induce donor specific tolerance without impairing the host defences or increasing the susceptibility to infection from all types of organisms.

The most common immunosuppressants prescribed for solid organ transplant recipients are:

- ***Calcineurin Inhibitors:***
  - ***Cyclosporine***
  - ***Tacrolimus***
- ***Mycophenolic Acids:***
  - ***Mycophenolate Mofetil***
  - ***Mycophenolate Sodium***
- ***Azathioprine***
- ***Sirolimus***
- ***Prednisone***
- ***Basiliximab***
- ***Anti-thymocyte Globulin***

Each of these drugs has its own adverse effect and toxicity profile that may result in serious morbidity or mortality. Careful management of these complications by the patient and the transplant team is critical to transplant success.

BC Transplant funds the following outpatient immunosuppressants for solid organ and pancreatic islet cell transplant recipients who have BC Medical Services Plan coverage and are registered with BC Transplant, when the guidelines are followed:

Outpatient Immunosuppression:

- Calcineurin Inhibitors:
  - Cyclosporine
  - Tacrolimus IMMEDIATE Release
  - Tacrolimus EXTENDED Release
- Mycophenolic Acids:
  - Mycophenolate Mofetil
  - Mycophenolate Sodium
- Azathioprine
- Sirolimus
- Prednisone

Inpatient Immunosuppression

BC Transplant funds the inpatient immunosuppressant basiliximab and entanercept for pancreatic islet cell transplant when the guidelines are followed.

Special Outpatient Medications Required to Maintain Transplant

In addition to immunosuppressants, solid organ transplant recipients often require other outpatient medications which are needed to maintain the integrity of the transplant and are very important in a patients' medication regimen. BC Transplant covers the cost of the following medications if the guidelines are met:

Erythropoiesis - Stimulating Agents:

- Erythropoietin
- Darbepoetin

Anti-Viral Agents:

- Valganciclovir
- Lamivudine
- Adefovir
- Tenofovir
- Entecavir
- Leflunomide

Anti-lymphocyte polyclonal antibody (ATG)

INTRODUCTION

Anti-thymocyte globulin (ATG) is a pasteurized solution of rabbit-derived polyclonal IgG antibodies directed against human T cells, produced by immunization of rabbits with human lymphocytes.
This monograph will focus on its use in solid organ transplants. ATG is funded by the inpatient pharmacy drug budget and not covered by BC Transplant.

MECHANISM OF ACTION

ATG is potent immunosuppressant and immunomodulator whose mechanisms of action are not fully understood.

The mixture of antibodies recognize key receptors on T-cells, resulting in complement-dependent T-cell lysis and opsonisation of T-cells with subsequent phagocytosis by macrophages. Thymopoiesis is also impaired, resulting in a decrease in the number of newly formed T-cells. This causes a substantial drop in the number of circulating T-cells, hence reducing the risk of organ rejection.

The usual magnitude is a greater than 90% reduction in the number of circulating T-cells. The duration of lymphopenia lasts around 3 months for most patients, though some have had sustained lymphopenia for over 1 year post-ATG.

ATG has shown benefits for patients at high risk of delayed graft function (DGF), potentially due to reducing ischemia-reperfusion injury by inflammatory mediators produced from T-lymphocytes.

PHARMACOKINETICS

Absorption / Onset:

T-cell depletion is usually noted within 1 day of the first ATG dose.

Distribution:

The volume of distribution of ATG is approximately 2 times plasma volume.

Distribution into breast milk is unknown, though other immunoglobulins do enter breast milk.

Metabolism:

Likely removed via opsonisation by the reticuloendothelial system if bound to T-cells, or via human antibody production.

Elimination:

Plasma half-life is variable (1.5 to 30 days[5], usually 2 to 3 days).

ATG remains active for days to weeks post-treatment.

The primary route of elimination is via cellular uptake with subsequent proteolytic degradation. Hence, no dosage adjustment is required in renal or hepatic impairment.

THERAPEUTIC USE

ATG is used at induction of immunosuppression to prevent transplant rejection in patients:

- at high immunological risk of rejection (i.e. recipients with greater than 80% calculated panel-reactive antibodies (cPRA), or those who have previously rejected one or more transplants within 1 year post-transplant)
- at high risk of delayed graft function due to DCD or ECD donors.
    - DCD: donation after cardiac death, ECD: expanded criteria donor (donor age greater than 60 years old, or donors aged 50 to 59 with 2 of the 3 features: hypertension, terminal Scr >132 umol/L, or death resulting from stroke.

- Low and intermediate immunological risk patients are generally treated with basiliximab for induction.

ATG is also administered for the treatment of acute rejection.

CONTRAINDICATIONS

Known hypersensitivity to rabbit proteins or any ingredient of the formulation, history of anaphylaxis with ATG, Epstein-Barr Virus mismatch, and acute infections which contraindicate further immunosuppression.

DRUG INTERACTIONS

Live vaccinations should not be administered to patients taking ATG or within 6 weeks of their scheduled transplant.
ATG has additive risks of infection and malignancy when used in combination with other immunosuppressants.

ADVERSE DRUG REACTIONS

Cytokine release syndrome associated with ATG administration frequently causes high grade fevers (over 39º C), chills and possibly rigors during or shortly after infusion. In severe cases, cardiorespiratory depression and death may rarely occur. To prevent or minimize febrile reactions, patients should be pre-treated with antipyretics (acetaminophen 650mg to 1000mg) and/or antihistamines (diphenhydramine 25mg to 50mg), and / or corticosteroids (methylprednisolone). Slowing the infusion rate may also be of benefit. For pediatric patients, acetaminophen 15 mg/kg/dose, diphenhydramine 1 mg/kg/dose.

Anaphylaxis occurs in less than 1% of patients. It may occur at any time during therapy and may present as hypotension, respiratory distress, or pain in the chest, flank, or back. If anaphylaxis occurs, the preparation should be discontinued immediately and standard treatments started (e.g. epinephrine).

Serum sickness has been reported in 5 to 10% of patients, which presents as fever, rash, arthralgias and / or myalgias. This usually occurs within 5 to 15 days of ATG therapy.

Thrombocytopenia and leukopenia occur in about 14% and 30% of patients respectively. Severe and prolonged lymphocytopenia may last over 1 year.

Due to the substantial drop in the number of circulating T-cells, infection and malignancy risk are significantly increased. Infections include bacterial, fungal, and viral infections with potential reactivation of latent infections (e.g. CMV); infections can be severe and may present as sepsis, so prophylaxis against certain infections such as CMV and PCP is essential if clinically indicated. Malignancies such as lymphoma and post-transplant lymphoproliferative disorder (PTLD) are significantly more common than basiliximab.

Other frequently reported adverse effects (incidence >25%) include fever, chills, diarrhea, headache, myalgias, nausea, peripheral edema, shortness of breath, weakness, tachycardia, and hypertension.

Area of Effect	Adverse Effect
CNS	Chills (55-57%), fever (46%), headache 27-40%), pain (26%), insomnia (12-20%), malaise (9-13%), serum sickness (2%)
CV	Hypertension (27-37%), tachycardia (23%), peripheral edema (20%), hypotension (10-16%)
Resp	Dyspnea (15-26%)
GI	Abdominal pain (17-38%), nausea (29-37%), diarrhea (20%), vomiting (20%), constipation (15%)
GU	None
Endo	None
Derm	Rash (7-13%), diaphoresis (6-13%), acne (12%) Injection site reactions (pain, erythema, swelling)
MSK	Myalgia (11-20%), arthralgia (15%), weakness (13%)
Heme	Leukopenia (49-57%) Neutropenia Lymphopenia (>90%) Thrombocytopenia (29-37%) Anemia (12%) Malignancy (e.g. PTLD, lymphoma) (4%)
ID	Infections (bacterial, fungal, viral, protozoal) (17%) Reactivation of latent infections (e.g. CMV – 13%) Sepsis (12%)
Other	Hypersensitivity reactions Infusion reactions / cytokine release syndrome

DOSE AND ADMINISTRATION

Most studies using ATG have based dosing calculations on actual body weight. Some preliminary studies have suggested that using ideal body weight results in similarly low rates of acute rejection with lower cost and fewer adverse effects, but this strategy requires further evaluation before it should become a new standard of practice.

Prophylactic antiviral therapy (e.g. valganciclovir) and antimicrobial therapy (e.g. nystatin mouth wash, sulfamethoxazole-trimethoprim) should be given during ATG therapy, if indicated.

Doses should always be rounded down to the nearest 25 mg increment.

The degree of lymphopenia may be helpful to assess the degree of T-cell depletion.

Dose reductions:

Reduce ATG dose by 50% if white blood cells (WBCs) are between 2 to $3x10^9$ cells/L or if platelets are between 50 to $75x10^9$ cells/L.

Consider holding or discontinuing ATG if WBCs are less than $2x10^9$ cells/L or platelets are less than $50x10^9$ cells/L.

Kidney Transplant Recipients:

Induction for high immunologic risk transplant candidates (i.e. cPRA ≥80%):

ATG 1.5 mg/kg IV daily for 4 days, ideally given intra-operatively

Total cumulative ATG dose of 6 mg/kg.

Induction for high donor risk (high risk for delayed graft function):

ATG 1 mg/kg IV daily for 3 days, ideally given intraoperatively

Total cumulative ATG dose of 3 to 4.5 mg/kg as per patient clinical status

Treatment of acute rejection:

ATG 1.5mg/kg IV daily. Total cumulative ATG dose of 6.0 to 7.5mg/kg.

Administration

ATG must be diluted by pharmacy in 50 to 500mL of isotonic solution (saline or dextrose) to a final concentration of approximately 0.5 mg/mL. It should be administered by slow IV infusion daily through a central line, using an automated pump. The initial dose should be administered over a minimum of 6 hours, with subsequent infusions over 4 hours if well-tolerated. Refer to hospital's IV manual for detailed administration guidelines.

Safety is not established for peripheral line administration, and there is an increased risk of deep vein thrombosis and thrombophlebitis. If there is no alternative other than a peripheral line, "administration via peripheral line" must be written as a component of the order, so that pharmacy can add 20mg hydrocortisone and 1000 units heparin to the IV solution of saline (dextrose may cause precipitant and is no longer recommended). If peripheral line is not specified, hydrocortisone and heparin will NOT be added, risking complications.

AVAILABILITY

Antithymocyte globulin rabbit (Thymoglobulin® Genzyme Corporation) is available in 25 mg/5 mL vials for injection.

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Azathioprine

INTRODUCTION

Azathioprine is an immunosuppressant antimetabolite that belongs to the thiopurine drug class and may be used in combination protocols. In the past azathioprine was used routinely for maintenance therapy to prevent rejection following solid organ transplantation. Azathioprine is no longer used routinely in post-transplant immunosuppression protocols but may be used in certain circumstances.

MECHANISM OF ACTION

Azathioprine is a purine analog that is incorporated into cellular DNA, where it inhibits purine nucleotide synthesis and interferes with the synthesis and metabolism of RNA.

PHARMACOKINETICS

Azathioprine is well absorbed from the gastrointestinal tract. Azathioprine is a prodrug for mercaptopurine. The thiopurine S-methytransferase (TPMT) is involved in the metabolism of all thiopurines and is one of the main enzymes that inactivates mercaptopurine. Azathioprine is primarily metabolized to two active metabolites: 6-mercatopurine and 6-thionosinic acid. Only one to two percent of the drug is eliminated unchanged by the kidneys.

THERAPEUTIC USE

Azathioprine may be used as maintenance therapy in conjunction with other immunosuppressive agents to prevent organ transplant rejection in patients who are unable to tolerate the gastrointestinal effects of mycophenolic acids, have an increased incidence of infection while on mycophenolic acids or in female transplant recipients who are considering pregnancy.
Prior to initiating azathioprine therapy it is recommended thiopurine S-methyltransferase (TPMT) genotyping be determined. This allows for patients at increased risk for myleosuppression to be identified, for starting dose of azathioprine to be reduced, or an alternative therapy to be prescribed. TPMT testing must receive Health Insurance of BC approval. Refer to LifeLabs website

Kidney and Kidney/Pancreas Transplant Recipients

Physicians must consult the patient's primary transplant centre if azathioprine is being considered. Azathioprine may be used in patients who cannot tolerate the gastrointestinal toxicity of mycophenolate mofetil, have an increased incidence of infection while on mycophenolate mofetil, or in female transplant recipients who are considering pregnancy. Azathioprine is not a preferred immunosuppressant in a patient who is on a steroid-free protocol.

Lung Transplant Recipients

Mycophenolate mofetil has replaced azathioprine post-transplant. There are some patients currently receiving azathioprine who have an intolerance to mycophenolate. If patients are stable on azathioprine there is no benefit to switching them to mycophenolate mofetil.

Heart Transplant Recipients
Mycophenolate mofetil has replaced azathioprine post-transplant. There are some patients currently receiving azathioprine who have an intolerance to mycophenolate. If patients are stable on azathioprine there is no benefit to switching them to mycophenolate mofetil.

Liver Transplant Recipients
TPMT genotyping will not be done in liver transplant recipients.

ADVERSE DRUG REACTIONS

Azathioprine Adverse Drug Reactions

Area of Effect	Adverse Effect	Symptoms
Hematologic	***Bone marrow depression Infection	Leukopenia Megaloblastic anemia Pancytopenia Thrombocytopenia
Gastrointestinal	Nausea and vomiting Anorexia Diarrhea Ulceration of oral mucosa Esophagitis with possible ulceration Steatorrhea	
Hepatic	Hepatotoxicity Hepatic veno-occlusive disease	Increased alkaline phosphatase Increased bilirubin
Other	Alopecia Retinopathy Hypersensitivity reaction Rash, fever Serum sickness Arthralgias Cutaneous effects Pulmonary effects Hypotension Pancreatitis	

*** Bone marrow depression is dose dependent and may be reversed by reducing the dose of azathioprine. However, people who inherit two non-functional TPMT alleles universally experience life-threatening myleosuppression. For this reason it is recommended TPMT genotyping or phenotyping be done prior to starting azathioprine. Dean L. Azathioprine therapy and TPMT genotype. Medical Genetics Summaries, Bethesda: National Center for Biotechnology

DRUG INTERACTIONS

Xanthine oxidase inhibitors (allopurinol and febuxostat (Uloric®) :
Azathioprine is metabolized by xanthine oxidase. Xanthine oxidase inhibitors (allopurinol and febuxostat) may inhibit azathioprine metabolism, thus resulting in increased azathioprine activity and toxicity when administered concurrently. If possible, concurrent use of xanthine oxidase inhibitors and azathioprine should be avoided. If concurrent use is required, the azathioprine dose should be reduced and the patient carefully monitored for bone marrow suppression.

Concurrent use of angiotensin-converting enzyme inhibitors (i.e., captopril, enalapril) may induce anemia as well as severe leukopenia.

Azathioprine may inhibit the anticoagulant effect of warfarin.

DOSE AND ADMINISTRATION

ADULT Kidney Transplant Recipients
If azathioprine is to be used, a maintenance adult dose of approximately 1.5 mg/kg/day PO is given once daily. Dosages are adjusted according to the white blood cell count. Decrease dose for white blood cell count less than 3.0 x 10^9/L.

PEDIATRIC Kidney Transplant Recipients
If azathioprine is to be used, the initial pediatric azathioprine dose is 3 to 5 mg/kg/day IV or PO once daily. Maintenance dose is 1 to 3 mg/kg/day IV or PO once daily.

ADULT Liver Transplant Recipients
If azathioprine is to be used, initial adult dosage of azathioprine is 1 mg/kg/day PO given once daily, rounded off to the nearest 25 mg. Dosages are adjusted according to the white blood cell count.

ADULT Lung Transplant Recipients
If azathioprine is used, the maintenance adult dose is approximately 1.5 to 2 mg/kg/day PO, rounded off to the nearest 25 mg. Consider reducing the dose if the patient has gastrointestinal intolerance or the white blood cell count is less than 3.0 x 10^9/L. Reduce dose by 2/3 to 3/4 if allopurinol is begun.

ADULT Heart Transplant Recipients
If azathioprine is used, the maintenance adult dose is 25 to 100 mg PO daily.

AVAILABILITY

Azathioprine is available for oral use as a 50 mg tablet or in 100 mg vials for intravenous use. Azathioprine tablets are available from several drug manufacturers.

Basiliximab

INTRODUCTION

Basiliximab is a monoclonal antibody, which is produced by recombinant DNA technology. It has been developed to overcome the shortcomings of the murine anti-TAC monoclonal antibodies (OKT_3), that is, a short half-life, requiring repeated doses which frequently result in the development of human anti-murine antibodies.

Basiliximab is a chimeric antibody in which the murine constant region of the immunoglobulin is replaced by human amino acid sequences.

Basiliximab is constructed by combining mouse variable regions with the constant region of human IgG1 immunoglobulin. Basiliximab is less immunogenic and has a much longer half-life than the murine monoclonal antibodies [1].

Basiliximab inhibits thymus-dependent lymphocyte proliferation by inhibition of interleukin-2 receptors. Interleukin-2-receptor antagonists have been shown to reduce the incidence of acute graft rejection in renal transplant recipients without increasing the incidence of opportunistic infections or malignancy [1-3].

Basiliximab has been shown to reduce renal transplant rejection within 6 months of transplant in low-risk patients [4-9].

MECHANISM OF ACTION

Basiliximab binds to the alpha chain of the IL-2 receptor on the surface of activated T-lymphocytes. It functions as a competitive inhibitor of IL-2, inhibiting mediated stimulation of lymphocytes, a critical event in the process of allograft rejection. By binding specifically to activate T-lymphocytes, inactive T-lymphocytes are not affected [1,5,7].

PHARMACOKINETICS

The mean initial concentration of basiliximab ranges from 5 to 10 microgram/mL. Basiliximab volume of distribution in the central compartment is reported to be 3.1 or 4.9 L in adults and 1.7 L in children, consistent with blood and plasma distribution [5, 8]. The terminal elimination half-life is estimated to be between 7 and 14 days [2, 5, 8]. Body weight or gender does not affect clearance. Among adult patients, elimination half-life is not influenced by gender, age (20 to 69 years) or race. Compared to adults, children (2 to 15 years old) have a lower clearance and longer half-life (11.5 days [5, 8]). The plasma concentration necessary to saturate IL-2 receptors is approximately 0.2 microgram/mL. After two doses of basiliximab, the duration of saturation of IL-2 receptors was four to six weeks in adult kidney transplant recipients [4-8].

THERAPEUTIC USE

Basiliximab is indicated for the prophylaxis of acute renal transplant rejection as part of an induction immunosuppressive regimen. The safety and efficacy of basiliximab has been investigated in kidney transplant clinical trials that have compared it to placebo in patients receiving cyclosporine and steroids [2, 4, 6, 8, 9].

The safety and efficacy of basiliximab has been reported in liver transplant recipients. Several clinical trials comparing basiliximab to placebo have demonstrated a lower rate of rejection in patients receiving cyclosporine, azathioprine and steroids [10-12].

The trials have concluded that the addition of basiliximab result in a reduction in the number of rejection episodes compared with a placebo or historical control with no increased of malignancies, infections, or other side effects [2, 4, 6, 8-12].

Kidney and Kidney-Pancreas Transplant Recipients

Basiliximab is indicated for prophylaxis of kidney transplant rejection in the following patients immediately post-transplant:

- Kidney and kidney-pancreas recipients from deceased or living donors with one or more HLA mismatch.
- Kidney and kidney-pancreas recipients who are defined as “low” and “intermediate” risk. “Intermediate risk” recipients are those patients who have received a previous transplant, or are a multi-organ recipient.
- Basiliximab is usually not indicated for kidney and kidney-pancreas recipients who are considered “high-risk” as defined by a PRA of 80 or greater and/or previous transplant lost within one-year post transplant. Basiliximab may be prescribed in high risk patients at the discretion of the nephrologist. If basiliximab is not indicated, high-risk patients should receive anti-thymocyte globulin as induction therapy.

Basiliximab is indicated for prophylaxis of kidney transplant rejection in the following patient’s for calcineurin inhibitor (CNI) replacement therapy. Prior to beginning basiliximab for CNI replacement, physician must submit in writing to BC Transplant, patient criteria for use. Each case will be considered on a case-by-case basis.

Patient must have:

- confirmed CNI nephrotoxicity (biopsy-proven)
- serum creatinine does not decrease in response to a decrease in CNI dose
- an increase of serum creatinine greater than 50% over baseline
- patient’s glomerular filtration rate must be less than 40 mL/min
- patient must not be in a clinical trial

Liver Transplant Recipients
Basiliximab is for standard induction therapy in liver transplant recipients with impaired renal function, in patients with a risk of developing renal dysfunction, and in patients whom are not able to tolerate calcineurin inhibitors early post-transplant. Impaired renal function is defined as a creatinine clearance of less than 50 mL/min or a serum creatinine greater than 150 micromole/L at time of transplant. The use of calcineurin inhibitors can be delayed until renal function has recovered after transplantation.

Lung Transplant Recipients
Basiliximab is indicated for prophylaxis of transplant rejection in all lung transplant recipients.

Basiliximab may be considered under exceptional circumstances in patients with calcineurin inhibitor (CNI) toxicity. Prior to beginning basiliximab for CNI replacement, physician must submit in writing to BC Transplant, patient criteria for use. Each case will be considered on a case-by-case basis.

Heart Transplant Recipients
Basiliximab is indicated for prophylaxis of transplant rejection in all heart transplant recipients immediately post-transplant.

The heart transplant team does use basiliximab for other indication which include sparing calcineurin inhibitors pre and post-surgery to prevent nephrotoxicity. The use of basiliximab in these cases is not currently funded by BC Transplant.

ADVERSE DRUG REACTIONS

Although data is limited, basiliximab is well tolerated. Administration of this agent has not been associated with significant clinical toxicity or cytokine release syndrome (fever, chills, headache, and pulmonary edema), which is commonly observed with muromonab-CD3 therapy. Adverse effects observed among patients treated basiliximab are similar to those treated with placebo [5, 6]. However, hypersensitivity reactions can occur. Medications for hypersensitivity reactions should be available for immediate use during the administration of these agents [7].

Administration of basiliximab does not appear to influence the frequency or severity of known immunosuppressive effects. Incidence of infection and frequency of malignancy, including lymphoproliferative disorders, was not increased when compared to placebo [5-8]. No clinically relevant changes in leukocyte counts or absolute lymphocyte counts have been noted during treatment [5, 6]. A small percentage (1.4%) of patients have developed anti-idiotype antibodies when treated with basiliximab. Detection of anti-idiotype antibodies was not associated with increased rejection or adverse reactions [5, 6, 8].

The effects of basiliximab on fertility and fetal harm are unknown. Basiliximab cannot be recommended for use in pregnancy unless the potential benefits outweigh potential risk to the fetus [7].

DRUG INTERACTIONS

No drug interactions have been reported. Basiliximab does not appear to interact pharmacokinetically with cyclosporine or tacrolimus. No significant increase in adverse reactions has been reported with basiliximab in combination with corticosteroids, azathioprine, acyclovir or ganciclovir [5-8].

DOSE AND ADMINISTRATION

ADULT Kidney and Kidney-Pancreas Transplant Recipients

For adults and adolescents 15 years old and older: 20 mg IV given on day 0, prior to transplant surgery (ideally intra-operatively), followed by 20 mg IV given on day 4 after transplantation [7].

PEDIATRIC Kidney Transplant Recipients

For adolescents and children 2 to 15 years old: 12 mg/m^2 IV (minimum 10 mg/dose, maximum 20 mg/dose) given on day 0, prior to transplant surgery, followed by 12 mg/m^2 IV (maximum 20 mg/dose) given on day 4 after transplantation.

Each dose should be diluted with 5 mL sterile water for injection to dissolve the powder. The reconstituted solution is diluted in 50 mL of normal saline or dextrose 5% in water (D5W).

ADULT Liver Transplant Recipients

20 mg IV given on day 0, either intra-operatively or immediately after transplant surgery, followed by the second dose, 20 mg IV given on day 4 after transplantation.

ADULT Lung Transplant Recipients

20 mg IV given on day 0, intra-operatively, followed by the second dose, 20 mg IV given on day 4 after transplantation.

ADULT Heart Transplant Recipients

20 mg IV given on day 0, intra-operatively, followed by the second dose, 20 mg IV given on day 4 post transplantation.

The heart transplant team does use basiliximab for other indications which include sparing calcineurin inhibitors pre and post- surgery to prevent nephrotoxicity. The use of basiliximab in these cases is not currently funded by BC Transplant.

AVAILABILITY

Basiliximab (Simulect® Novartis Pharmaceuticals) is available as a powder for reconstitution for IV use in 20 mg/5 mL vials [7].

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Cyclosporine

INTRODUCTION

Cyclosporine is a potent immunosuppressant used for the prophylaxis and treatment of graft rejection following solid organ transplantation. The narrow therapeutic range and variability of the pharmacokinetics of cyclosporine requires monitoring of blood concentrations in the management of transplant recipients.

MECHANISM OF ACTION

The immunosuppressive effect of cyclosporine is mediated through inhibition of T-lymphocyte function with minimal activity against B-cells. The precise biochemical mechanisms involved are not yet known. It is known that cyclosporine inhibits the production and release of interleukin II (T-cell growth factor) from activated T-helper cells. Interleukin II is necessary for the induction of cytotoxic T-lymphocytes in response to antigen challenge. The development of interleukin II receptors on precursor cytotoxic T-cells are also inhibited. This inhibition results in decreased proliferation of activated cytotoxic T-cells, the cells responsible for the rejection of transplanted tissue.

In contrast, cyclosporine has little effect on the activation and proliferation of suppressor T-cells. B-cell differentiation and function, required for normal antibacterial defences, appear to be resistant to cyclosporine. As a result of the selectivity of cyclosporine, it is possible to suppress T-cell mediated cellular immunity without adversely affecting the B-cell mediated humoral immunity.

PHARMACOKINETICS

Cyclosporine Neoral® is a microemulsion formulation. The absorption phase for cyclosporine occurs over the first 4 hours after oral administration. This phase is characterized by rapid changes in blood cyclosporine concentrations and a high degree of inter- and intra-patient variability. This phase demonstrates the individual patient's capacity to absorb cyclosporine from the gastrointestinal tract, which is dependent on concurrent medications, integrity of the gastrointestinal tract and other patient-specific factors. Cyclosporine Neoral® is distributed largely outside the blood volume. In the blood, 33 to 47% is present in plasma, 4 to 9% in lymphocytes, and 41 to 58% in erythrocytes. In plasma, approximately 90% is bound to proteins, mostly lipoproteins. Cyclosporine Neoral® is extensively metabolized to approximately 15 metabolites. There is no single metabolic pathway. Elimination is primarily biliary, with only 6% of the oral dose excreted in the urine; only 0.1% is excreted in the urine as unchanged drug. The half-life of cyclosporine is approximately 18 hours (range 7.7 to 26.9 hours) with a high variability reported on depending on the assay used and type of transplant patient has received.

THERAPEUTIC USE

Cyclosporine is approved for solid organ transplant rejection prophylaxis and treatment. Cyclosporine may be used alone or in combination with other immunosuppressants.

CONTRAINDICATIONS

Cyclosporine is contraindicated in all patients with a hypersensitivity to cyclosporine.

ADVERSE DRUG REACTIONS

Nephrotoxicity

The most frequently reported adverse effect of cyclosporine is reversible nephrotoxicity. Elevated cyclosporine blood concentrations are thought to increase the risk of nephrotoxicity. Cyclosporine nephrotoxicity is particularly troublesome in renal transplant recipients as it may be difficult to differentiate from graft rejection. The incidence of nephrotoxicity increases when cyclosporine is administered with other nephrotoxic agents, including amphotericin B and aminoglycosides.

Other Side Effects

Other frequently observed side effects include hypertension, hirsutism, tremors, gingival hyperplasia and hepatotoxicity. Hypertension may be difficult to control in these patients and is seen most frequently in cardiac transplant recipients (53% versus 13 to 26% in renal transplant recipients). Hirsutism may be treated with depilatory creams, electrolysis, or shaving. Gingival hyperplasia may be controlled by proper oral hygiene and regular dental check-ups. Both hirsutism and gingival hyperplasia are reversible upon discontinuation of cyclosporine. Hepatotoxicity, manifested by an increase in direct and total bilirubin, is also reversible upon dose reduction or discontinuation of the drug.

Hypersensitivity

Hypersensitivity reactions have been reported in patients receiving intravenous cyclosporine. Symptoms include flushing, shortness of breath, hypotension and anaphylaxis. The reaction is believed to be due to poly-oxyethylated castor oil (cremophor-E), a surfactant present in IV solution. Patients who have experienced a hypersensitivity reaction while on IV cyclosporine have subsequently received oral cyclosporine without a reaction.

Cyclosporine Adverse Drug Reactions

Area of Effect	Adverse Effect	Lab Results
Renal	Nephrotoxicity	Increased urea Increased serum creatinine Hyperkalemia Hyperuricemia Decreased serum $HC0_3$
Cardiovascular	Hypertension	Hypomagnesemia
Nervous System	Tremors * Seizures * Headache * Paresthesia * Confusion *	
Dermatologic	Hirsutism Gingival hyperplasia Acne	
Hepatic	Hepatotoxicity	Abnormal liver function Increased serum bilirubin
Gastrointestinal	Diarrhea Nausea and vomiting Anorexia Abdominal discomfort Gastritis Hiccups Peptic ulcer	
Infectious	Pneumonia Septicemia Abscesses Urinary tract, viral, local and systemic fungal infections Skin and wound infections	Increased white blood cell count
Hematologic	Leukopenia Anemia Thrombocytopenia Lymphoproliferative diseases	Abnormal haematological tests
Sensitivity Reactions	Anaphylactic response to IV Cyclosporine*	
Other	Hyperlipidemia Sinusitis Gynecomastia Edema Fever Hearing loss	

* Rare

DRUG INTERACTIONS

Cyclosporine interacts with many drugs (see following table). Drugs that inhibit liver microsomal enzyme function can impair the metabolism of cyclosporine, leading to increased cyclosporine blood concentrations and toxicity. Alternatively, enzyme-inducing drugs increase the metabolism of cyclosporine and may result in lowered cyclosporine blood levels and increased risk of transplant rejection.

Important Drug Interactions of Cyclosporine (CSA), Tacrolimus (TAC) and Sirolimus

(Prepared by Nilu Partovi, Clinical Pharmacy Specialist, Vancouver General Hospital, November 2008)

The table outlines major drug interactions only, and is not all-inclusive. The majority of interactions are the result of effects on the cytochrome P450 3A4 enzyme. Medications included below should be avoided when an appropriate alternative exists. If no alternatives are available, please advise the transplant clinic so that appropriate blood work can be arranged or advised. For a complete list of drug interactions, refer to tertiary references.

Drug A) Drugs that **DECREASE** CSA/TAC/ Sirolimus levels	**Possible Mechanism / Onset and severity**	**Adverse Effects**	**Management**
Anticonvulsants: ▪ phenytoin ▪ carbamazepine ▪ phenobarbital, primidone	Enzyme induction ↑ CSA/TAC/sirolimus metabolism • delayed / major • delayed/ moderate • delayed / major	↓ effectiveness of CSA/TAC/sirolimus which may lead to rejection	↑ CSA/TAC/sirolimus dose by 30% and monitor levels following addition, dose change or discontinuation.
Antimicrobial: ▪ rifampin ▪ caspofungin **(tacrolimus ONLY)**	Induction of hepatic enzymes • delayed / major Mechanism is unknown • delayed/ moderate	Same as above	Monitor CSA/TAC/sirolimus levels following addition, dose change or discontinuation. Monitor tacrolimus level closely when caspofungin is initiated or dose changes and when caspofungin discontinued.

Important Drug Interactions of Cyclosporine (CSA), Tacrolimus (TAC) and Sirolimus cont

B) Drugs that **INCREASE** CSA/TAC/ Sirolimus levels			
Antimicrobial: ▪ erythromycin, clarithromycin (Biaxin®) ▪ azole antifungals (fluconazole, ketoconazole, itraconazole, posaconazole, voriconazole)	↓ CSA/TAC/sirolimus metabolism, ↑ rate of absorption, ↓volume of distribution • delayed / major ↓CSA/TAC/sirolimus metabolism • delayed/ moderate	↑ CSA/TAC/sirolimus levels, ↑ risk of toxicity	Monitor CSA/TAC/sirolimus levels following addition, dose change or discontinuation. Monitor serum creatinine
Antidepressants: fluoxetine, fluvoxamine greater than sertraline, venlafaxine, mirtazapine, paroxetine	↓ CSA/TAC/sirolimus metabolism • delayed/ moderate	↑ CSA/TAC/sirolimus levels, ↑ risk of toxicity	Consider another antidepressant (citalopram, escitalopram) and/or monitor CSA/TAC/sirolimus levels closely
Cardiovascular: ▪ diltiazem, verapamil ▪ amiodarone	May inhibit hepatic metabolism of CSA/TAC/sirolimus •delayed / Major	↑CSA/TAC/sirolimus levels, ↑ risk of toxicity	Monitor CSA/TAC/sirolimus levels following addition, dose change or discontinuation.

Pharmacodynamic Interactions of Cyclosporine (CSA), Tacrolimus (TAC) and Sirolimus

Drug	Proposed Mechanism and Possible effects	Management
Aminoglycosides, Amphotericin B, NSAIDS, C0X-2 inhibitors **(CSA and tacrolimus ONLY)**	Additive nephrotoxicity	These drugs should be avoided in transplant recipients due to increased nephrotoxicity. The only exception is when the benefit clearly outweighs the potential risks and only used for short-term treatment. Renal function should be monitored closely while these drugs are used with cyclosporine or tacrolimus.
HMG-CoA Reductase Inhibitors: Example: lovastatin, simvastatin, atorvastatin	CSA/TAC/sirolimus may ↓ metabolism of these agents →accumulation of statin and toxicity Myalgia, myopathy, rhabdomyolysis	Start with low dose of these agents and monitor very closely for toxicity
Digoxin	↓ volume of distribution of digoxin by 50-70%, ↑ digoxin half-life by 30-40%, and increased digoxin levels digoxin toxicity such as vomiting, cardiac arrhythmia's	Initiate low dose and follow up with serum digoxin levels Closely monitor for symptoms of digoxin toxicity
nifedipine phenytoin **(cyclosporine ONLY)**	Additive incidence of gingival hyperplasia with CSA (not tacrolimus) Incidence increases from 8% (CSA alone) to 51% (combination)	Avoid long term use if possible. Good dental/oral hygiene with regular dentist visits

DOSE AND ADMINISTRATION

The cyclosporine dose will vary according to the dosage form, type of transplant, patient factors, time post- transplant and hospital protocols. Dosage must be individualized for the best therapeutic effect with minimal toxicity.

Cyclosporine is not prescribed in liver transplant recipients with hepatitis C or renal dysfunction.

The route of cyclosporine **administration** depends on the type of transplant received and the patient status. Immediately post-transplant heart, pancreas and kidney transplant patients receive intravenous cyclosporine. Oral cyclosporine is administered as soon as oral intake is tolerated. Patients with malabsorption syndromes or liver transplants should receive intravenous cyclosporine therapy until adequate absorption can be ensured. The intravenous dose of cyclosporine (Sandimmune IV®) is one third the oral cyclosporine (Neoral®) dose.

Intravenous cyclosporine (Sandimmune IV®) should be diluted in 5% dextrose in water or normal saline to a final concentration of 0.5 to 2.5 mg/mL. To minimize flushing, paresthesia and nausea, administer cyclosporine slowly, either as a 24 hour continuous infusion, or over 4 to 6 hours, depending on the clinical situation.

Oral cyclosporine (Neoral®) is available both in capsule and liquid form. The solution should be used within two months of opening the amber glass container. Once the solution has been measured with an oral syringe, the dose may be mixed with milk, apple juice or orange juice to mask the bitter taste (in a glass or ceramic cup only). ***Do not*** use grapefruit juice as the drink, as grapefruit juice has been shown to inhibit cyclosporine metabolism, thus increasing cyclosporine concentrations. The same drink should be mixed with the cyclosporine each time. Once mixed, the solution should be taken immediately.

For patients requiring a switch from cyclosporine to tacrolimus, an estimated conversion of 40:1 (cyclosporine dose to tacrolimus) can be used a starting point.

Therapeutic Drug Monitoring

Cyclosporine has a narrow therapeutic index; thus therapeutic drug monitoring is required.

Cyclosporine exposure as determined by the area under the concentration time curve (AUC_{0-12}) has been shown to correlate with clinical events.

Studies demonstrate that the AUC in transplant patients is ideal for minimizing cyclosporine toxicity and promoting its efficacy. However, full AUC measurements are impractical for use as a monitoring tool in a clinical setting.

Evidence shows that the monitoring of cyclosporine at the 2 hour concentration point (C_2) is the most accurate single time point for assessment of cyclosporine absorption and immunosuppressive effect. By monitoring C_2 target concentrations in renal and liver transplant recipients one can more accurately adjust the patients' cyclosporine dose to

minimize toxicity and rejection rates. However C_2's are not done in all patients, some program use cyclosporine trough concentration measurements.

In British Columbia the tandem mass spectrometry is the assay used for the determination of cyclosporine blood concentrations. The assay is done at Vancouver General Hospital, St. Paul's Hospital, Victoria General Hospital, Penticton Regional Hospital and LifeLabs®. Blood for cyclosporine assays from Northern Health is sent to Vancouver General Hospital and from Interior Health is sent to Penticton Regional Hospital. The tandem mass spectrometry assay results are 24% lower than the TDX Immunoassay which was previously used. When reviewing the literature it is important to know which assay was used in the trial.

Target Cyclosporine Blood Concentrations for Solid Organ Transplant Recipients

Time Post Transplant (Months)	Cyclosporine Trough Concentration (ng/mL) Tandem Mass Spectrometry Assay	Cyclosporine C_2 Concentration (ng/mL) Tandem Mass Spectrometry Assay
ADULT Kidney and Kidney Pancreas Transplant Recipients (Oct 2014)		
Less than 1 months	300 to 350	1300
1 to 2 months	250 to 300	1100
3 to 6 months	150 to 250	800 to 900
7 to 12 months	125 to 200	700
Greater than 12 months	75 to 125	450-600
PEDIATRIC Kidney Transplant* Recipients (Oct 2014)		
Less than 1 months	200 to 250	Not used
1 to 2 months	150 to 200	Not used
2 to 3 months	100 to 150	Not used
Greater than 3 months	80 to 100	Not used
**as per Dr. Matsell November 1 2012*		
ADULT Liver Transplant Recipients (May 2021)**		
0 to 3 months	200 to 250	Not used
3 to 12 months	150 to 200	Not used
Greater than 12 months	100 to 125	Not used
** **Cyclosporine C_2** is not routinely used in liver transplant recipients		
ADULT Lung Transplant Recipients (Nov 2014)		
Less than 1 months	275 to 300	Not used
1 to 3 months	250 to 275	Not used
3 to 6 months	200 to 250	Not used
6 to 12 months	150 to 200	Not used
Greater than 12 months	125 to 150	Not used
Greater than 12 month with decrease in renal function	Switch to tacrolimus if possible	

Target Cyclosporine Blood Concentrations for Solid Organ Transplant Recipients cont'd

Time Post Transplant (Months)	Cyclosporine Trough Concentration (ng/mL) Tandem Mass Spectrometry Assay	Cyclosporine C_2 Concentration (ng/mL) Tandem Mass Spectrometry Assay
ADULT Heart Transplant * (Nov 2014)**		
When eGFR is greater than 45 mL/min/1.73 m^2		
Less than 1 month	Not used	1200 to 1400
2 to 3 months	Not used	1000 to 1200
4 to 5 months	Not used	800 to 1100
6 to 12 months	Not used	700 to 1000
12 to 24 months	Not used	600 to 800
Greater than 24 months	Not used	400 to 600
When eGFR is less than 45 mL/min/1.73 m^2		
Less than 1 month	Not used	1000 to 1200
2 to 3 months	Not used	800 to 1100
4 to 5 months	Not used	700 to 900
6 to 12 months	Not used	600 to 800
12 to 24 months	Not used	400 to 600
Greater than 24 months	Not used	300 to 400
Patients Transplanted Greater Than 15 Years Ago		
0 to 3 months	300 to 350	Not used
3 to 6 months	200 to 300	Not used
6 to 12 months	150 to 250	Not used
Greater than 12 months	100 to 150	Not used

*** MOTOWN study used immunoassay not tandem mass spectrometry assay to analyze cyclosporine concentrations

Dose Adjustments for Adult Patients
For C_2 levels to be useful they must be taken exactly 2 hours after the cyclosporine dose. If the level is not taken at exactly the correct time with respect to the dose, cyclosporine doses may be adjusted to the detriment of the patient.

For patients who have been stable, a dosage change is rarely recommended based on a single cyclosporine C_2 or trough level.

To ensure correct dose adjustment use the following guidelines:

1. Ensure that the following measurements have been done within one month prior to any dose adjustment: blood pressure, serum creatinine, serum urea and lipid levels.

2. If the patient is stable, had no rejections and no transplant complications continue with the current cyclosporine dose and continue to monitor the patient.

3. If the patient has suspected problems with the absorption of cyclosporine, has cyclosporine nephrotoxicity, or has had a rejection, measure the C_2 concentration:

   a) If the **C_2 concentration is consistently lower** than the target (at two consecutive concentrations), and the patient is stable (i.e. no history of multiple or recent rejections), the dosage may be left unchanged or increased carefully on the basis of clinical criteria.

   b) If the **C_2 concentration is consistently higher** than the target (at two consecutive concentrations), and the patient is not stable (i.e. history of recent or recurrent rejection) the dosage may be left unchanged or decreased carefully on the basis of clinical criteria.

Be cautious that the change in dosage is reasonable; normally a dosage change is not greater than 50 mg/day increments.

AVAILABILITY

Oral cyclosporine (Neoral® Novartis Pharmaceuticals) is available both in capsule and liquid form. The capsules are supplied in 10 mg, 25 mg, 50 mg and 100 mg strengths. The solution contains 100 mg/mL cyclosporine microemulsion. The solution should be used within two months of opening the container.

Cyclosporine (Sandimmune® Novartis Pharmaceuticals) is available as a concentrate for intravenous use 50 mg/mL, in 1 mL and 5 mL ampules.

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Erythropoiesis-Stimulating Agents Darbepoetin/Erythropoietin

INTRODUCTION

Darbepoetin alpha is a hyper glycosylated erythropoiesis-stimulating protein, produced by recombinant DNA technology. It is indicated for the treatment of anemia associated with chronic renal failure, including patients on dialysis and not on dialysis. Darbepoetin has a longer terminal half-life than erythropoietin which allows for less frequent dosing [(1)].

MECHANISM OF ACTION

Darbepoetin stimulates erythropoiesis by the same mechanism as endogenous erythropoietin. Erythropoietin is a glycoprotein that is the primary regulator of erythropoiesis with specific interaction with the erythroid receptor on the erythroid progenitor cells in the bone marrow. The production of erythropoietin primarily occurs in and is regulated by the kidney in response to changes in tissue oxygenation. Darbepoetin binds to the erythropoietin receptors on burst forming units erythroid (BFU-e) and colony forming units erythroid (CFU-e), which divide and eventually differentiate into mature circulating red blood cells [(1)].

PHARMACOKINETICS

Following intravenous (IV) administration to adult chronic renal failure patients, darbepoetin serum concentration-time profiles are biphasic, with a distribution half-life of approximately 1.4 hours and mean terminal half-life of approximately 21 hours. Following subcutaneous administration, the absorption is slow and rate limiting, and the terminal half-life is 49 hours (range: 27 to 89 hours), which reflects the absorption half-life. The peak concentration occurs at 34 hours (range: 24 to 72 hours) post subcutaneous administration in adult chronic renal failure patients, and bioavailability is approximately 37% (range: 30% to 50%). The distribution of darbepoetin in adult CRF patients is predominantly confined to the vascular space (approximately 60 ml/kg). The pharmacokinetics of darbepoetin does not change as a function of time/dose. Steady state levels are achieved within 4 weeks [(1)].

A single dose, randomized, double blind study was conducted to compare the pharmacokinetics of IV epoetin to IV darbepoetin. Eleven patients receiving chronic ambulatory peritoneal dialysis (CAPD) received a single IV dose of either epoetin (100 units/kg) or an equivalent dose of darbepoetin based on peptide mass. After a 28-day washout period, patients received a single IV injection of the alternate drug. The half-life of IV darbepoetin was three fold longer than IV erythropoietin, 25.3 hours vs. 8.5 hours, respectively (p=0.0008). In the second phase of this study the half-life of SC darbepoetin was determined to be 48.8 hours. In comparison to erythropoietin, the area under the curve was greater and the clearance lower for darbepoetin. There was no significant difference in the volume of distribution of these two drugs and the bioavailability of SC injection is very similar [(2)]. Other evaluations indicate that the pharmacokinetics of darbepoetin are similar in adult and pediatric patients with chronic renal failure [(3)].

THERAPEUTIC USE

The erythrocyte stimulating agents (darbepoetin and erythropoietin) are indicated for the following kidney and kidney-pancreas transplant recipients:

Criteria for ESA: (based on BC Renal Agency CKD non-dialysis anemia recommendations)
Patients NOT on dialysis who have a failing kidney transplant,

- Have at least one symptom of anemia (fatigue, excessive intolerance, angina, impaired cognition)
- Must meet all the following lab criteria:
  - GFR less than 50 mL/min by eGFR (eGFR based on MDRD equation)
  - Hemoglobin less than 95 g/L
  - Transferrin saturation (TSAT) 22% or greater

As there is inconclusive evidence on the use of erythrocyte stimulating agents with delayed graft function, each patient will be reviewed on a case by case basis by the Director of Renal Transplant Program at one of the transplant centres in BC.

For pediatric transplant patients being followed at Transplant Centre at BC Children's Hospital will not be required to submit ESA approval requests to BCT.

Erythrocyte stimulating agents are not indicated for patients who have anemia due to causes other than anemia associated with chronic renal failure. This includes gastrointestinal bleeding, folate and iron deficiencies, hemolysis or underlying hematologic disease [(1)]. BC Transplant does not fund darbepoetin for these patients.

Darbepoetin or erythropoietin are not intended for patients who require immediate correction of severe anemia or emergency transfusions. Blood pressure should be adequately controlled prior to initiation of darbepoetin therapy and must be closely monitored and controlled during treatment.

Therapeutic End Goal: Target hemoglobin 95-115 g/L

Target TSAT 22% or greater: Suggest iron studies 1 month after ESA start, then every 3 months (refer to page 2 on BC Renal Agency anemia protocol)

- If hemoglobin is between 85-94 g/L, check iron studies. For TSAT less than 22% consider iron therapy. If no dose increase of ESA in past 5 week, increase ESA dose per BCPRA protocol and monitor at regular blood work cycle.
- If hemoglobin is between 95-115 g/L, maintain ESA and monitor at regular blood work cycle
- If hemoglobin is between 116-125 g/L, if no dosage reduction of ESA in past 5 weeks, reduce ESA dose per BC Renal Agency protocol and monitor at regular blood work cycle.
- If hemoglobin is between 126-139 g/L, hold ESA. Measure hemoglobin every 2 weeks. If hemoglobin is above 126 g/L after 12 week off ESA, discontinue ESA.

(See Appendix C: BCT Fax Form: Application for Erythrocyte Stimulating Agents) Is to be completed and sent to BCT from the Transplant Clinics prior to beginning ESA.

ADVERSE DRUG REACTIONS

The safety profile of darbepoetin was assessed in 1578 chronic renal failure patients treated with this drug and compared to 591 patients treated with erythropoietin[4]. Adverse events were comparable in incidence, type and severity between the two treatments and the majority of these were due to the underlying disease process. There was no evidence that the safety profile of darbepoetin differed in patient subgroups or changed with time [1, 4].

Darbepoetin Adverse Drug Reactions

Area of Effect	Adverse Effects
Cardiac	Congestive heart failure, cardiac arrhythmia, hypertension, hypotension
Body	Sepsis, headache
Gastrointestinal	Diarrhea, nausea
Musculoskeletal	Myalgia
Other	Vascular access thrombosis

As of October 2002, over 92,000 patients have been treated with darbepoetin, representing over 50,000 patient years of exposure to the drug [5]. To date, there are no reports of antibody mediated pure red cell aplasia (PRCA) cases caused by darbepoetin.

Despite the longer half-life of darbepoetin no drug accumulation was observed over time. [6] Compared to erythropoietin there was no difference in the rate of decline in hemoglobin following cessation of therapy due to higher than target hemoglobin levels [7,9].

Darbepoetin is contraindicated in patients with: uncontrolled hypertension, known hypersensitivity to the active substance or any of the excipients or sensitivity to mammalian cell-derived products [1].

DRUG INTERACTIONS

No formal drug interaction studies of darbepoetin with other medications commonly used in chronic renal failure patients have been performed, however, there are no known drug interactions reported [1].

DOSE AND ADMINISTRATION

Starting Dose

The recommended starting dose of darbepoetin for the correction of anemia in patients with chronic renal failure is 0.45 mcg/kg administered as a single IV or subcutaneous injection once weekly [1]. Because of individual variability, doses should be titrated to a target not to exceed a hemoglobin concentration of 120 gram/L [1]. In a study by Toto et al, 608 epoetin naïve,

predialysis patients were successfully managed with darbepoetin given subcutaneously every 2 weeks at a starting dose of 0.75 mcg/kg rounded to the nearest available fixed dose [8].

Due to the possibility of ESA's causing an increase in blood pressure and adverse cardiac events in patients with a hemoglobin greater than 130 g/L, use the lowest dose to maintain an upper haemoglobin target of 100 g/L. Dosage reduction is required if hemoglobin is above 130 g/L.

Dosing When Switching to Darbepoetin from Erythropoietin

Clinical studies demonstrated that the relationship between baseline erythropoietin and maintenance darbepoetin is nonlinear across the dosing spectrum [1, 9]. Consequently, the starting weekly dose of darbepoetin should be estimated on the basis of the weekly erythropoietin dose at the time of substitution. Due to the longer serum half-life Darbepoetin should be administered less frequently than erythropoietin. Patients receiving erythropoietin 2 or 3 times a week should change to once weekly Darbepoetin at a dose equivalent to their total weekly dose of erythropoietin. Patients receiving erythropoietin once per week should change to darbepoetin once every 2 weeks at a dose that is equivalent to the sum of 2 weekly doses of erythropoietin. The same route of administration should be used. For patients prescribed prefilled syringes the calculated dose should be rounded upward to the next available syringe strength [1]. In darbepoetin clinical trials, a dose conversion of 200 units of erythropoietin for 1 mcg of darbepoetin was used and was shown to be an appropriate starting dose for darbepoetin. The following chart shows a conservative approach to starting darbepoetin when switching from erythropoietin and in most instances, the darbepoetin dose will likely need to be titrated upwards to achieve target hemoglobin levels.

Estimated Darbepoetin (Aranesp®) Starting Dose (mcg/week) Based on Previous Erythropoietin (Eprex®) (units/week) [1]

Previous Weekly Erythropoietin Dose (units/week)	Weekly Darbepoetin Dose (mcg/week)
less than 2,500	6.25
2,500 to 4,999	12.5
5,000 to 10,999	25
11,000 to 17,999	40
18,000 to 33,999	60
34,000 to 89,999	100
90,000 and greater	200

Administration
Darbepoetin can be administered by either the intravenous (IV) or subcutaneous route [(1)].

Monitoring
When darbepoetin therapy is initiated or adjusted, the hemoglobin should be followed weekly until stabilized and monitored at least monthly thereafter [(1)].

Availability
Darbepoetin (Aranesp® Amgen Inc.) is available as a human serum albumin free formulation in single use prefilled syringes (PFS) in the following doses: 10, 20, 30, 40, 50, 60, 80, 100, 130, 150, 200, 300, 500mcg/syringe [(1)].

Erythropoeitin (Eprex, Janssen) is available in for following strengths: 1000, 2000, 3000, 4000, 5000, 6000, 8000, 10000, 20000, 30000 and 40000 unit/syringe

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Filgrastim (G-CSF)

MANAGEMENT OF POST-TRANSPLANT LEUKOPENIA/NEUTROPENIA

Background:
Solid organ transplant recipients commonly experience low white blood cell counts (neutropenia) post-transplant. The cause of neutropenia is usually due to bone marrow suppression effects of anti-rejection and antiviral transplant medications or infections such as cytomegalovirus (CMV) related to transplantation. Patients with very low neutrophil counts are at very high risk for severe infections which require hospital admission, antibiotics and therapy with filgrastim. The addition of filgrastim to BC Transplant's drug formulary would enable transplant clinicians the ability to treat patients with severe neutropenia as outpatients, decreasing the risk of infection and rejection, and the costs associated with inpatient admission.

The management of neutropenia post-transplant involves a careful assessment of the cause(s) of neutropenia and adjustments in immunosuppressive regimens and/or anti-viral therapies if CMV is suspected as the cause of the neutropenia. The most common medication adjustment includes reduction in the anti-metabolite (mycophenolate/azathioprine) dose to allow for neutrophil count recovery. However, there are many cases where a reduction in anti-metabolite dose is not the optimal choice as it can pose an increased risk of graft rejection. Clinicians are challenged with balancing neutropenia and the risk of infection versus immunosuppression reduction and risk of graft rejection. In some clinical situations where the risk of rejection and the consequences of rejection are extreme, the use of filgrastim will allow the continuation of anti-rejection treatment.

Evidence for filgrastim use in solid organ transplants:

Although not extensively studied, filgrastim has been used to increase neutrophil counts in solid organ transplant patients. Schmaldienst et al studied 19 renal transplant patients that experienced leukopenia in the 2 weeks to 24 months after transplantation (1). In comparison to an age-matched historical control group, patients receiving filgrastim had shorter duration of leukopenia (1.29 versus 7 days), with fewer infections; in addition, there were no episodes of rejection 2 weeks following administration.

Turgeon et al retrospectively reviewed 50 renal or liver transplant patients (2). Of the 50 patients, 43 patients had a rise in the leukocyte count to greater than 5.0 X 10^9/L following filgrastim. In 81.6% of cases, filgrastim therapy allowed for recommended dosing of ganciclovir or valganciclovir for treatment of CMV-induced neutropenia. Most recently, an abstract presented by Poon et al at the American Transplant Congress 2016 demonstrated effective reversal of neutropenia in kidney transplant recipients without increasing the risk of rejection (3).

Protocol:

The BC Transplant Drug Strategy Advisory Committee, and PHSA leadership and Finance have approved the addition of filgrastim to the BC Transplant Drug Formulary. With the support of the various organ group specialists/clinicians, BC Transplant has established the proposed protocol **Appendix D** as outlined in Appendix 1 of that document.

Clinicians are required to complete the **data collection-prescription form (Appendix 2).** The BC Transplant Pharmacy will dispense the filgrastim and fax the form to BC Transplant for data collation. An annual report will be presented to the Drug Strategy Advisory Committee summarizing the usage and clinical data. If a patient requires more than 2 courses in a 12 month period, please contact the pharmacist at BC Transplant.

References

1. Schmaldienst S, Bekesi G, Deicher R, Franz M, Hörl WH, Pohanka E. Recombinant human granulocyte colony-stimulating factor after kidney transplantation: a retrospective analysis to evaluate the benefit or risk of immunostimulation. Transplantation. 2000 Feb 27;69(4):527-31.

2. Turgeon N, Hovingh GK, Fishman JA, Basgoz N, Tolkoff-Rubin NE, Doran M, Cosimi AB, Rubin RH. Safety and efficacy of granulocyte colony-stimulating factor in kidney and liver transplant recipients. Transpl Infect Dis. 2000 Mar;2(1):15-21.

3. Poon T, Guerra C. Evaluation of the Utilization of Filgrastim in Kidney Transplant Recipients. [abstract]. *Am J Transplant.* 2016; 16 (suppl 3). http://www.atcmeetingabstracts.com/abstract/evaluation-of-the-utilization-of-filgrastim-in-kidney-transplant-recipients/.

Management of Neutropenia Post Transplant v2.2

Post transplant neutropenia could be related to CMV, mycophenolate, azathioprine, valganciclovir*, Septra (cotrimoxazole).
The primary transplant specialists should be consulted regarding changes in immunosuppression and the re-introduction of antimetabolites, Septra when neutropenia has resolved. Decreasing or stopping anti-rejection medications in the "high risk" for rejection patient needs careful consideration.

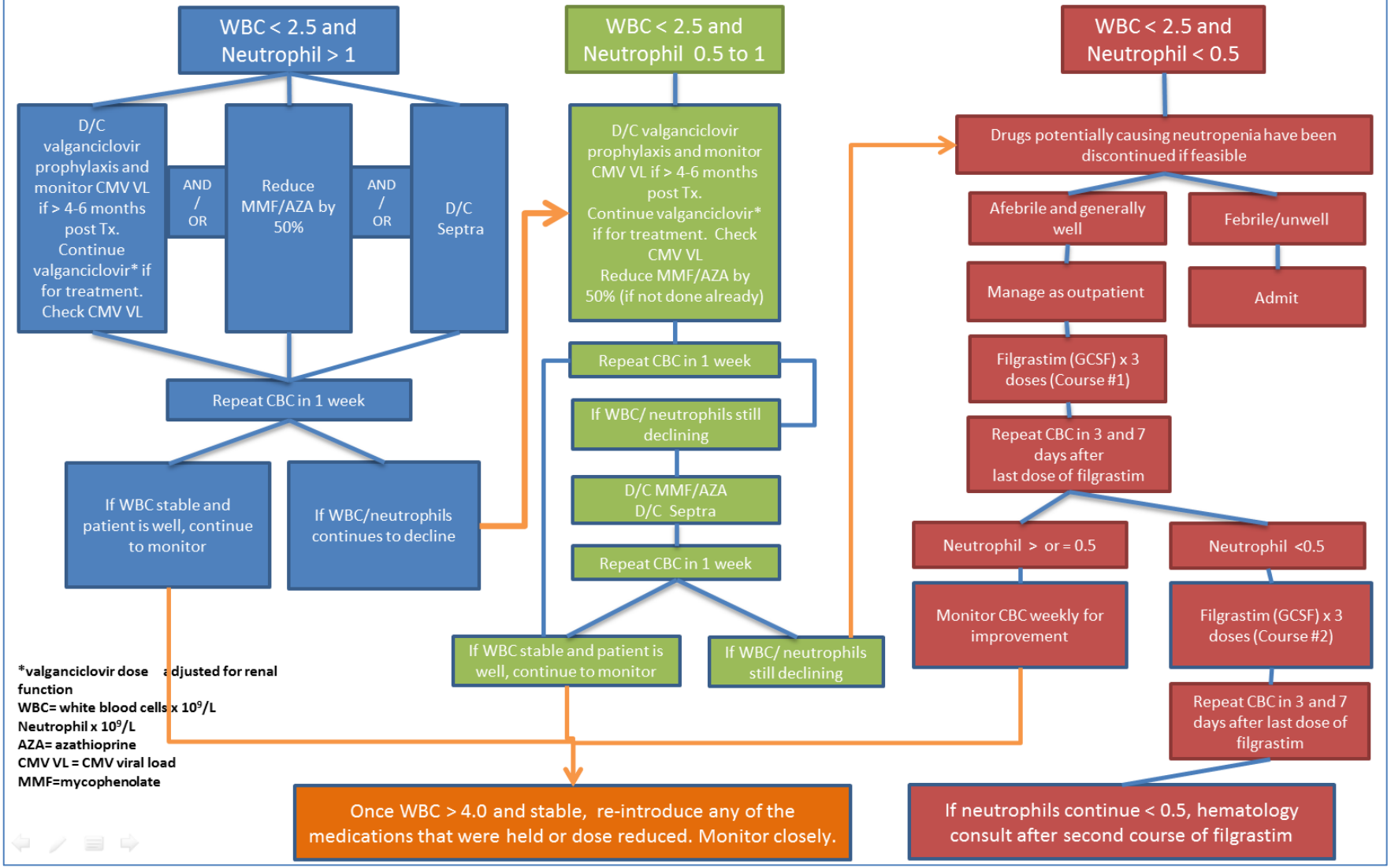


Table of Contents

Filgrastim (G-CSF, Grastofil) Data Collection-Prescription

1. Provider/Clinic to complete data collection sections and to forward prescription to BC Transplant Pharmacy

2. BC Transplant Pharmacy to dispense and fax form to BC Transplant office *Fax: 604-877-2111*

Organ group: ☐ Heart ☐ Kidney ☐ Liver ☐ Lung ☐ Pancreas/Islet Requesting clinic: _____

Assessment: please include dose adjustments if applicable

(dd-mmm-yy)	Date:	Date:	Date:	Date:	Date
WBC: (10^9/L)					
Neutrophil: (10^9/L)					
azathioprine					
cyclosporine					
cotrimoxazole (SS) 400/80					
mycophenolate (MMF / sodium)					
prednisone					
sirolimus					
tacrolimus (BID / OD)					
valganciclovir					

Indication(s) for filgrastim:
☐ Neutrophil < 0.5
☐ Febrile neutropenia
☐ Other: _____
☐ If transplant medication adjustments cannot be made, please indicate reason:
_____

Prescription: ☐ 1st course – recommend 300 mcg dose for first course
☐ 2nd course

*If neutrophils not responding after 2nd course in a 12 month period, please consult BCT and hematology
*For pediatric patients at BC Children's – please supply Neupogen brand filgrastim

☐ filgrastim (Grastofil) 300 mcg SC daily X 3 days

☐ filgrastim (Grastofil) 480 mcg SC daily X 3days

Pharmacy: ☐ VGH ☐ SPH ☐ BCCH ☐ RJH ☐ Abb ☐ Nan ☐ Lang ☐ Kam ☐ Kel ☐ Pen ☐ PG ☐ Trl ☐ Sur

_____

Prescriber signature Print Name College ID Date

Pharmacy: Please fax completed form to BC Transplant office: Fax: 604-877-2111 Attn: Pharmacy Coordinator

Hepatitis B Antiviral Agents:
Entecavir, Tenofovir*, and Lamivudine

INTRODUCTION

Patients undergoing liver transplantation for hepatitis B virus (HBV) infection require ongoing antiviral therapy post transplantation. In the absence of HBV prophylaxis, recurrence of HBV occurs in approximately 80% of liver transplant recipients within four years post-liver transplant. Current treatments do not eradicate the virus. The aim of therapy for chronic hepatitis B is to achieve long-term suppression of the HBV DNA to prevent disease progression leading to cirrhosis and hepatocellular carcinoma. Effective therapy for the liver transplant recipient with chronic HBV infection includes administration of life-long oral antiviral agents in combination with Hepatitis B Immunoglobulin (HBIG).

Currently entecavir and tenofovir are considered first line antiviral agents for the treatment of chronic hepatitis B infection due to their excellent efficacy and high barrier to resistance. Lamivudine and adefovir are no longer recommended due to high incidence of resistance with continued use. Patient adherence to medication is critical to achieve adequate HBV DNA suppression and prevent resistance.

NOTE: *Tenofovir disoproxil fumerate (TDF) - currently funded by BC Transplant
Tenofovir alafenamide (TAF) is only available through BC Transplant Compassionate Funding approval process.

ANTIVIRAL THERAPEUTIC USE GUIDELINES

A. Chronic Hepatitis B Virus Infection

Liver Transplant Recipients

BC Transplant covers the cost of outpatient HBV antiviral agents for patients post **liver transplant**.

HBV Antiviral Indications for Liver Transplant Program

HBV Antiviral Agent	Post-transplant indications
Entecavir	• first line therapy in HBV treatment - naïve patient • on entecavir prior to transplant • contraindicated if patient has a history of lamivudine resistance
Tenofovir	• first line agent in patients with lamivudine resistance • on tenofovir prior to transplant • caution when used in patients with renal dysfunction
Lamivudine	• Not recommended as first line agent. Might be used in exceptional cases.

Non-Liver Transplant Recipients with chronic HBV infection

- BC Transplant will cover the cost of outpatient HBV antiviral agents for patients who have confirmed chronic hepatitis B (HBsAg positive for at least 6 months) infection **post non-liver transplant** (regardless of HBV viral load) to avoid HBV reactivation with immunosuppressive therapy.

HBV Antiviral Indications for Non-Liver Transplant Program

HBV Antiviral Agent	Post-transplant indications
Entecavir	• on entecavir prior to transplant • recommended first line agent in HBV treatment- naïve patient • NOT recommended if history of lamivudine resistance
Tenofovir	• first line agent in patients with lamivudine resistance • on tenofovir prior to transplant • caution when used in patients with renal dysfunction
Lamivudine	• on lamivudine prior to transplant with no documented HBV lamivudine resistance

B. Hepatitis B Core Antibody Positive Donors and Recipients

BC Transplant covers the cost of **post-transplant** HBV antiviral agents for some recipients of liver and non-liver solid organ transplants depending on donor and recipient HBV core antibody status (in patients without active HBV replication) to avoid HBV reactivation with immunosuppressive therapy. HBV DNA testing should be done on all donors with HBV core antibody positive status.

This table refers to donors and recipients who are **HBsAg negative**. Generally, donors who are HBsAg positive would not be suitable donors, and recipients who are HBsAg positive would require life-long anti-viral therapy.

For living donor recipients, confirming immunity or immunizing to Hepatitis B is recommended prior to transplant.

Donor and Recipient: Hepatitis B Surface Antigen Negative

Organ Transplanted	Donor HBV Antibody Status	Recipient HBV Antibody Status	Anti-Viral Therapy Post Transplant
Liver	HBV core positive	HBV core positive or negative	Lamivudine for life
	HBV core negative	HBV core positive	Monitor for HBV reactivation* No prophylaxis
Non-liver	HBV core positive	HBV core negative (Regardless of HBV surface antibody status)	Monitor for HBV reactivation* No prophylaxis
	HBV core negative	HBV core positive	Monitor for HBV reactivation* May consider a referral to a hepatologist for ongoing monitoring

*Monitor for HBV reactivation at every 3 months for one year then every 6 months. If patient being treated for acute rejection, monitor for HBV reactivation every 3 months for 6 months. Tests to be done: liver enzymes, hepatitis B surface antigen, hepatitis B core antibody, hepatitis B surface antibody and hepatitis B DNA. If Hep B DNA detectable or HBsAg positive, consult transplant hepatology or infectious disease specialist.

ADVERSE DRUG REACTIONS

Entecavir, tenofovir and lamivudine are generally well tolerated. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues.

Severe exacerbations of hepatitis have been reported in patients who have discontinued HBV antiviral therapy.

HBV Antiviral Agent	Adverse Drug Reactions
Entecavir	Most common (greater than and equal to 3%) headache, fatigue, dizziness, and nausea
Tenofovir	Nephrotoxicity: Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia) Metabolic bone disease especially in children
Lamivudine	Most common adverse events (greater than 10%) malaise, fatigue, respiratory tract infections, headache, abdominal discomfort and pain, nausea, vomiting and diarrhea ALT elevations more common in patients treated with lamivudine than placebo

DRUG INTERACTIONS

Lamivudine
The likelihood of metabolic interactions with lamivudine is low due to limited metabolism, limited plasma protein binding and almost complete renal elimination of unchanged drug. Lamivudine is primarily eliminated by active organic cationic secretion. The possibility of interactions with other drugs administered concurrently should be considered when their main route of elimination is active renal secretion via the organic cationic transport system (e.g. trimethoprim).

There have been no observed clinically significant interactions in patients taking lamivudine concurrently with commonly used transplant immunosuppressants.

Entecavir
Entecavir is primarily eliminated by the kidneys, therefore co-administration of entecavir with drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of either entecavir or the co-administered drug. In clinical trials, co-administration of entecavir with lamivudine, adefovir dipivoxil or tenofovir disoproxil fumarate did not result in significant drug interactions. The effects of co-administration of entecavir with other drugs which are renally eliminated or are known to affect renal function have not been evaluated, and patients should be monitored closely for adverse events.

Entecavir is not a substrate, inhibitor or inducer of the CYP450 enzyme system, therefore the pharmacokinetics of entecavir are unlikely to be affected by co-administration with drugs that affect the CYP450 system.

Tenofovir
The potential for CYP450 mediated interactions involving tenofovir and other medications is low. Co-administration of tenofovir with drugs which are eliminated by active tubular secretion may increase serum concentrations of either tenofovir or the co-administered drug, due to competition for this elimination pathway. Drugs which decrease renal function may also increase serum concentrations of tenofovir.
Serious drug interactions have been reported with atazanavir and lopinavir/ritonavir and didanosine.

DOSE AND ADMINISTRATION

Liver Transplant Patients
Lamivudine, entecavir and tenofovir are administered orally once a day. Dosages must be adjusted in patients who have impaired renal function as these drugs are eliminated by renal excretion.
HBV antiviral therapy should be continued indefinitely in all patients post-transplant. The relationship between treatment with HBV antivirals and long-term outcomes (hepatocellular carcinoma, decompensated cirrhosis) is not known in transplant recipients.

Entecavir
Adult dose: 0.5 mg PO once daily on an empty stomach. To be used in treatment naïve patients or in those with lamivudine sensitive disease
Pediatric dose: not established

Adult Dosage Adjustment of Entecavir in Renal Impairment

Creatinine Clearance (mL/min)	Entecavir Dose in Patients with Lamivudine Sensitive HBV Disease
greater than and equal to 50	0.5 mg once daily
30 to 49	0.5 mg three times a week on Monday, Wednesday and Friday or q48hrs
10 to 29	0.5 mg twice a week on Monday and Thursday or q72hrs
Less than 10 (hemodialysis or chronic peritoneal dialysis patients)	0.5 mg every seven days. Give after hemodialysis

Tenofovir
Adult dose: 300 mg PO once daily with or without food.
Pediatric dose: not established

Adult Dosage Adjustment of Tenofovir in Renal Impairment

Creatinine Clearance (mL/min)	Tenofovir Dose
greater than 50	300 mg once daily
30 to 49	300 mg three times a week on Monday, Wednesday and Friday or q48hrs
10 to 29	300 mg every Monday and Thursday
less than 10	Not recommended
on hemodialysis	300 mg once weekly after dialysis (assume thrice weekly dialysis)

Lamivudine
Adult dose: 100 mg PO once daily with or without food
Pediatric dose: greater than two years of age, 3 mg/kg once daily to a maximum of 100 mg PO daily

Dosage Adjustment of Lamivudine in Adults with Renal Impairment

Creatinine Clearance (mL/min)	Lamivudine Dose
greater than 30	100 mg once daily
15 to 29	100 mg three times a week on Monday, Wednesday, Friday
less than 15	100 mg twice a week on Mondays and Thursdays
Hemodialysis patients	100mg twice weekly on Monday and Wednesday. On dialysis days, dose post dialysis

REFERENCES

1. EASL clinical practice guidelines. Management of chronic hepatitis B virus infection. J Hepatol. 2017 vol. 67 j 370–398.
2. Huprikar S, Danziger-Isakov L, Ahn J, et al. Solid organ transplantation from hepatitis B virus–positive donors: consensus guidelines for recipient management. Am J Transplant 2015;15:1162-1172.
3. D'Avola D, Herrero I. Prophylaxis and treatment of hepatitis B infection in the setting of liver transplantation. Rev Esp Enferm Dig 2011;103:142-149
4. Bzowej N, Han S, Degertekin B et al. Liver transplantation outcomes among Caucasians, Asian, Americans, and African Americans with hepatitis B. Liver Transpl. 2009;15:1010-20.
5. Lok ASF. Liver transplantation for chronic hepatitis B virus infection. April 2019. UpToDate www.uptodate.com
6. Jonas MM, Deirdre AK, Mizerski J et al. Clinical trial of lamivudine in children with chronic hepatitis B N Eng J Med 2002; 346:1706-1713.
7. Baraclude® (entecavir) product monograph, revised November 19, 2010, Bristol-Myers Squibb Canada, Montreal, Quebec
8. Heptovir® (lamivudine) product monograph, January 7, 2019, GlaxoSmithKline Inc. Canada, Mississauga, ON
9. Viread® (tenofovir disoproxil fumarate), June 13, 2018, Gilead Sciences, Inc. Mississauga, ON

Letermovir in Solid Organ Transplants

Background:

Letermovir (Prevymis[R], Merck Canada Inc.) was launched in Canada in Dec 2017, and marketed for CMV prophylaxis for allogeneic hematopoietic stem cell transplant HSCT (bone marrow transplant) based a double-blind, randomized placebo-controlled trial (Study P001, n=570). It's novel mechanism of action, inhibition of CMV DNA terminase complex results in the inhibition of viral maturation.[1] Letermovir spectrum of activity is specific to human CMV with no activity against HSV or VZV. It's favourable side effect profile suggests it does not have the same bone marrow suppressive activity as ganclovir/valganciclovir, nor the renal toxicity of foscarnet/cidofovir.

The recent CADTH (Canadian Agency for Drugs and Technologies in Health) review has recommended Provincial funding agencies consider reimbursement for prophylaxis of CMV for adult CMV R+ recipients for HSCT[2]. BC Pharmacare is currently reviewing letermovir for special authority support for HSCT CMV prophylaxis based on the CADTH recommendation. The report noted that despite the lack of published evidence, letermovir may be considered for off-label indications such as recurrent and/or resistant CMV, pre-emptive therapy and treatment for viremic patients.[2]

Evidence for letermovir use in solid organ transplants (SOT):

The evidence for letermovir use in solid organ transplants is very limited. The renal transplant group in Vancouver is going to be participating in a randomized controlled trial of letermovir vs valganciclovir for prophylaxis of CMV in high risk D+/R- kidney transplant recipients (NCT3443869). The results of this trial will help expand the prophylaxis indication to include solid organ transplants. Valganciclovir continues to be the drug of choice for both prophylaxis and treatment for ambulatory patients.[3]

There has been a Phase II study looking at using letermovir for pre-emptive therapy for CMV viremia, however, the doses used in that study were much lower than those currently used for the prophylaxis indication.[4] Letermovir is currently not approved for pre-emptive therapy or treatment of CMV disease.

Recommendation:

Letermovir's novel mechanism of action and favourable side effect profile may offer advantages over traditional antivirals. However, due to the lack of published evidence on letermovir for SOT (prophylaxis or treatment), it's low genetic barrier for resistance and it's high cost, BC Transplant Drug Strategy Advisory Committee supports the addition of letermovir to the BC Transplant Drug Formulary on a ***restricted basis.***

Clinicians are required to consult the Transplant Infectious Disease specialist to review therapeutic options for CMV prophylaxis/treatment. Letermovir is ***reserved for CMV primary/secondary prophylaxis*** (CMV viral load less than 35 IU prior to starting letermovir)

- CMV resistance to ganciclovir/valganciclovir
- Allergy to ganciclovir or valganciclovir
- Significant neutropenia (persistently less than 0.5 10^9/L) prior to CMV antiviral therapy despite filgrastim/G-CSF support and unable to reduce immunosuppression

If CMV viral load is above 35 IU/mL while on letermovir prophylaxis, discontinue letermovir and treat viremia using alternate CMV antivirals. Due to letermovir's lack of activity against HSV/VZV, additional antiviral therapy may be necessary.

An annual report will be presented to the Drug Strategy Advisory Committee summarizing the clinical criteria for usage and budget impact.

References:

[1] Infection and Drug Resistance 2015; 8: 269-277
[2] CADTH (Canadian Agency for Drugs and Technologies in Health) Drug Reimbursement Recommendation June 2018
[3] Transplantation. 2018 Jun; 102(6):900-931
[4] Transpl Int. 2014 Jan; 27(1):77-8

Letermovir Authorization Request

1. After ID consultation, provider/clinic to complete form and forward prescription to BC Transplant Pharmacy.

2. BC Transplant Pharmacy to fax form to BC Transplant office
Fax: 604-877-2111

3. Please wait for authorization prior to dispensing

BCT ID:

Name:

PHN:

Organ group: ☐ Heart ☐ Kidney ☐ Liver ☐ Lung ☐ Pancreas/Islet Requesting clinic:

Transplant Infectious Disease Consult: ☐ Yes ☐ No

Indication(s) for letermovir prophylaxis:

☐ CMV resistance to ganciclovir or valganciclovir
☐ Allergy to ganciclovir or valganciclovir
☐ Significant neutropenia (neutrophils persistently <0.5) prior to CMV antiviral therapy despite filgrastim/G-CSF support and unable to reduce immunosuppression
☐ Other: (with Transplant ID approval)

_____

NOTE: If CMV VL > 35 IU/mL, discontinue letermovir and treat viremia using alternate CMV antivirals. Additional HSV/VZV therapy may necessary as letermovir lacks of herpes virus activity.

Prescription: Letermovir (Prevymis®) - available in 28 day blister pack

- **Ensure BCT has authorized prior to dispensing**
- **Dispense maximum 4 week supply at a time; maximum 24 week total course authorization***

☐ first course ☐ subsequent course

☐ letermovir 480 mg PO daily for
☐ 4 weeks ☐ 12 weeks ☐ 24 weeks (max) ☐ _____ weeks

If patient is on cyclosporine:
☐ letermovir 240 mg PO daily for
☐ 4 weeks ☐ 12 weeks ☐ 24 weeks (max) ☐ _____ weeks

Pharmacy:
☐ VGH
☐ SPH
☐ BCCH
☐ RJH
(Victoria)

☐ Abbotsford
☐ Nanaimo
☐ Langley
☐ Kamloops
☐ Kelowna
☐ Penticton

☐ Prince George ☐ Trail ☐ Surrey ☐ Other

*If a patient requires extended durations greater than 6 months or additional courses, a separate application needs to be submitted.

Prescriber signature Print Name College ID Date

BCT Authorization: ☐ Yes ☐ No Date _____
Notes:_____

Please fax completed form to BC Transplant office: Fax: 604-877-2111 Attn: Pharmacy Coordinator

Mycophenolate Mofetil and Mycophenolate Sodium

INTRODUCTION

Mycophenolate mofetil and mycophenolate sodium are immunosuppressants used in combination with cyclosporine or tacrolimus and corticosteroids, as well as in steroid-free regimens. Mycophenolate mofetil significantly reduces acute rejection rates following renal transplantation [1-3]. Mycophenolate sodium is therapeutically equivalent to mycophenolate mofetil in renal transplant recipients [4-6]. However, **the two drugs are not interchangeable** as the rate of absorption following oral administration of the two medications is not equivalent.

MECHANISM OF ACTION

Mycophenolate mofetil is a semi synthetic prodrug that is rapidly hydrolyzed *in vivo* to form the active metabolite, mycophenolic acid (MPA) [7].

Mycophenolate sodium is an enteric-coated formulation which allows delayed release of MPA into the small intestine.

The active immunosuppressant agent of mycophenolate mofetil and mycophenolate sodium, MPA, is a potent, non-competitive, reversible inhibitor of inosine monophosphate dehydrogenase resulting in blockage of *de novo*, purine guanosine synthesis, selectively suppressing proliferation of T- and B-lymphocytes [8].

PHARMACOKINETICS

Mycophenolate mofetil is rapidly absorbed following oral administration and completely hydrolyzed to yield MPA, the active metabolite [7].

Mycophenolate sodium is an enteric-coated formulation which allows delayed release of MPA into the small intestine [8].

MPA is metabolized in the liver to form an inactive mycophenolic acid glucoronide (MPAG). MPAG undergoes enterohepatic recirculation giving rise to a secondary MPA peak concentration six to twelve hours after oral administration of mycophenolate mofetil. This helps to maintain sustained plasma concentrations of the drug.

Less than one percent of the dose is excreted as MPA in the urine. Approximately 87% of the administered dose is excreted in the urine as MPAG [7]. The time to reach peak concentrations of MPA is delayed (1.5 to 2.5 hours) with mycophenolate sodium compared to mycophenolate mofetil (1 hour), consistent with the release of MPA in the small intestine [8]. Mycophenolate mofetil and mycophenolate sodium are not interchangeable because the rate of absorption following oral administration of the two medications is not equivalent.

The half-life of MPA is approximately 11.7 to 17.9 hours [7, 8].

Mycophenolate sodium 720 mg and mycophenolate mofetil 1,000 mg can be considered equimolar in terms of mycophenolic acid [6, 8].

THERAPEUTIC USE

Mycophenolic acids are used in combination post-transplant immunosuppressive regimens to prevent solid organ transplant rejection.

Mycophenolate mofetil may be used in adults pre-kidney transplant in combination with tacrolimus, plasma exchange and rituximab for ABO incompatible recipients who may receive a living donor transplant.

Mycophenolate mofetil may be used in pediatric pre-transplant for recipients who may receive a living donor transplant.

The safety and efficacy of mycophenolate sodium and mycophenolate mofetil when used in combination with cyclosporine and steroids in renal and heart transplant recipients is comparable for at least one year post transplant in terms of outcomes [5][13-15].

CONTRAINDICATION

Pregnant Women: Mycophenolic acids are associated with an increased risk of first trimester pregnancy loss and congenital malformations if taken during pregnancy. Unplanned pregnancies in patients taking mycophenolic acids should be avoided to minimize fetal exposure. Mycophenolic acids should not be used in pregnant women unless the potential benefit to the fetus justifies the risk. Effective contraception should be used before beginning mycophenolic acids, during therapy and for six weeks following discontinuation of therapy, even when there has been a history of infertility [16, 18].

ADVERSE DRUG REACTIONS

Overall frequencies of adverse effects are similar between mycophenolate mofetil (2 gram/day) and mycophenolate sodium (1.44 gram/day) in both *de novo* and maintenance adult renal transplant recipients when used in combination with cyclosporine and corticosteroids [7, 8, 9].

Most Common Mycophenolic Acid Adverse Drug Reactions

Area of Affect	Adverse Effect
Gastrointestinal	Constipation* Diarrhea** refer to Management of Post -Transplant Diarrhea, page 45 Dyspepsia Nausea** Vomiting* Abdominal pain*
General	Edema Pain** Fever*
Hematologic	Bone marrow suppression Anemia*** Leukopenia**refer to Management of Post -Transplant Leukopenia, page 46
Infectious	Sepsis* Opportunistic (CMV) Urinary tract infection**
Nervous System Disorder	Insomnia* Tremor Headache

* Most common adverse effects (greater than and equal to 10%)

** Most common adverse effects (greater than and equal to 25%)

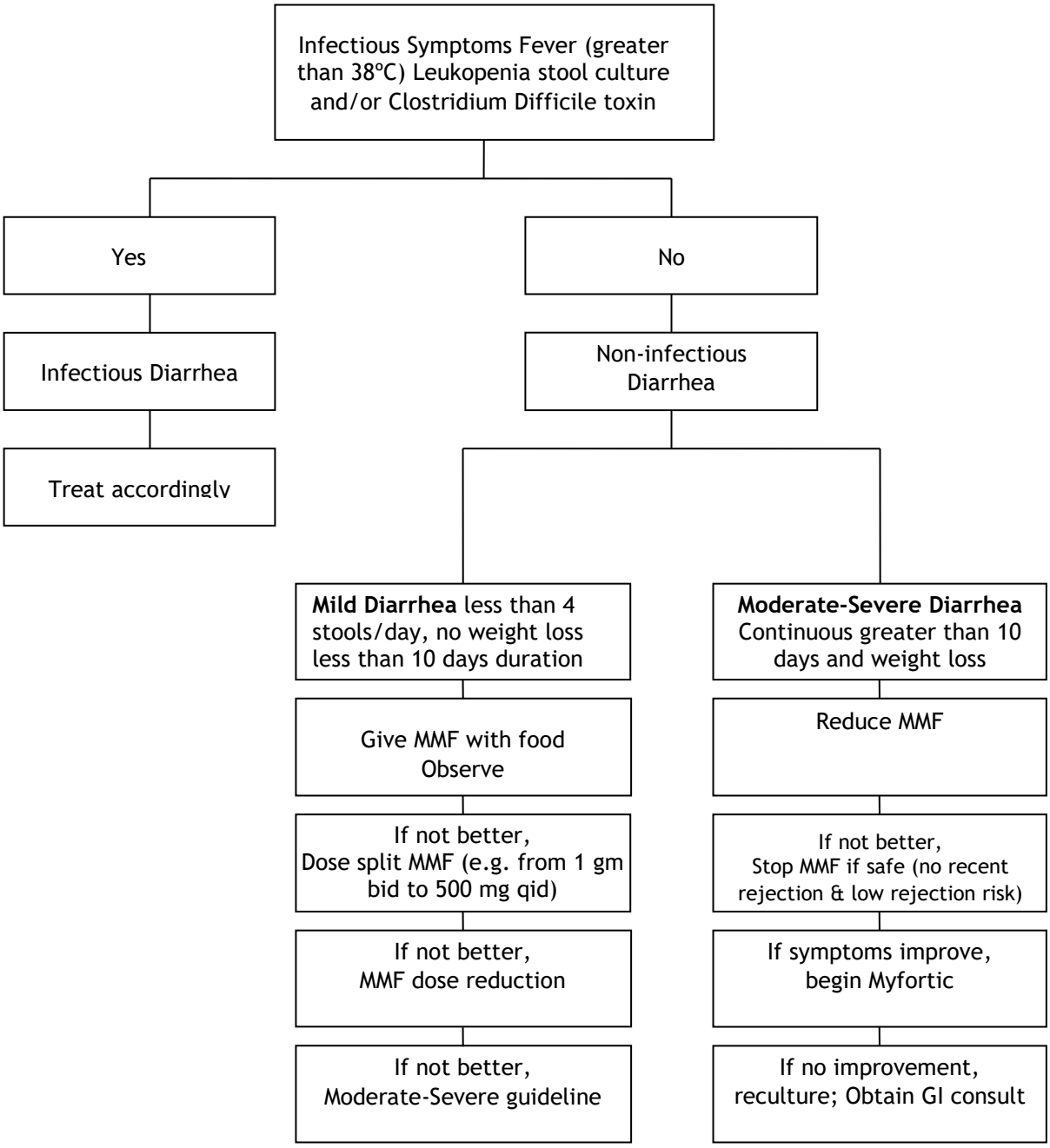
*** Cases of pure red cell aplasia (PRCA) type of anemia that develops secondary to failure of erythropoiesis have been reported in patients treated with mycophenolate in combination with other immunosuppressive agents. The mechanism for mycophenolate mofetil induced PRCA is not known. In some cases PRCA was found to be reversible with dose reduction or discontinuation of mycophenolate. In transplant recipients reduced immunosuppression may place the graft at risk [17].

Many of the common side effects are dose dependent and can be ameliorated by reducing or discontinuing the mycophenolate mofetil or mycophenolate sodium dose temporarily. However, this may leave the transplant recipient at increased risk of allograft acute rejection as a result of suboptimal immunosuppression [10, 11].

MANAGEMENT OF POST-TRANSPLANT DIARRHEA

Diarrhea is a frequent problem in post-transplant patients. One must make a distinction between medication induced and infectious diarrhea.

Treatment of Post-Transplant Diarrhea



References

Davies NM et al. Gastrointestinal side effects of mycophenolic acid in renal transplant patients: a reappraisal. *Nephrol Dial Transplant*. 2007: 22; 2440-2448.

Maes B et al. Severe diarrhea in renal transplant patients: results of the DIDACT study. *Am J Transplant.* 2006:6; 1466-1472.

DRUG INTERACTIONS

Magnesium and aluminum containing antacids may decrease the absorption of mycophenolate mofetil and mycophenolate sodium and should not be taken at the same time [8].

Cholestyramine (Questran®) and other medications that interfere with enterohepatic recirculation may decrease the absorption of the mycophenolate mofetil and should not be administered concurrently [8].

When mycophenolic acids are administered with acyclovir, ganciclovir, and valganciclovir, increased plasma concentrations of acyclovir, ganciclovir, and valganciclovir may occur due to competition for tubular secretion in the presence of renal failure [8]. Monitor carefully.

Azathioprine and mycophenolate mofetil inhibit purine synthesis. Azathioprine and mycophenolic acids should not be administered concomitantly [8].

There is a potential interaction between proton-pump inhibitors and mycophenolate sodium. Proton-pump inhibitors lower the gastric PH and increase the probability of early release of MPA in the stomach.

DOSE AND ADMINISTRATION

Mycophenolate mofetil is the standard mycophenolic acid used in the BC Transplant immunosuppressant protocols.

Mycophenolate Mofetil (generic brands)

ADULT Kidney and Kidney-Pancreas Transplant Recipients

The initial adult post-transplant dose of mycophenolate mofetil is 1 gram PO bid.
For adult patients requiring desensitization prior to a renal transplant, mycophenolate mofetil may be administered up to 14 days prior to transplant at a dose of 500 mg PO bid.

PEDIATRIC Kidney Transplant Recipients

The initial pediatric dose of mycophenolate mofetil is 600 mg/m^2/dose PO bid (up to a maximum total daily dose 2 gram daily). With pharmacokinetic monitoring, doses are individualized to optimize therapy for each patient.

- Body surface area of 1.25 to 1.5 m^2: mycophenolate mofetil 750 mg PO bid.
- Body surface area greater than 1.5 m^2: mycophenolate mofetil 1 gram PO bid [7].

Dose may be adjusted downwards if a patient has gastrointestinal intolerance.

For pediatric patients receiving a living donor transplant mycophenolate mofetil may be administered up to 14 days prior to transplant at a dose of 600 mg/m^2/dose PO bid (up to a maximum total daily dose of 2 gram daily).

ADULT Liver Transplant Recipients
For adults the initial mycophenolate dosage is 1 gram PO bid. Mycophenolate mofetil will be tapered with a view to discontinuing after three to five years post-transplant in select patients.

ADULT Lung Transplant Recipients
Initial immunosuppression will include mycophenolate mofetil. For adults the initial dose is 1.5 gram PO every 12 hours. In patients with gastrointestinal intolerance or if white blood cell count is less than 3 x 10^9/L consult the lung transplant team for dosage adjustment.

ADULT Heart Transplant Recipients
Initial immunosuppression will include mycophenolate mofetil 1 gram PO bid for all patients. Patients will remain on mycophenolate mofetil.

ADULT Pancreatic Islet Transplant Recipients
Standard immunosuppression for all adult pancreatic islet transplant recipients includes mycophenolate mofetil 1 gram PO bid.

Mycophenolate Sodium (generic brands)

In terms of mycophenolate sodium provided, 180 mg is equivalent to mycophenolate mofetil [250] mg, and mycophenolate sodium 360 mg is equivalent mycophenolate mofetil 500 mg [(8)].

ADULT Kidney and Kidney-Pancreas Transplant Recipients
Mycophenolate sodium may be prescribed for patients at the discretion of the physician or patients who are following out-of-province protocols.
The initial adult dose of mycophenolate sodium is 720 mg PO bid. Total daily dose is 1.44 gram [(8)].

PEDIATRIC Kidney Transplant Recipients
The initial pediatric dose of mycophenolate sodium is 400 to 450 mg/m^2 PO bid (total daily dose is 800 to 900 mg/m^2), rounded to the nearest capsule or tablet strength (maximum 720 mg per dose) [(12)].

Tablets should not be crushed, chewed or cut prior to ingesting. Tablets must be swallowed whole to maintain integrity of enteric coating [(8)].

ADULT Liver Transplant Recipients
Mycophenolate sodium may be prescribed for patients who are following out of province protocols or at the discretion of a physician.

ADULT Lung Transplant Recipients
Mycophenolate sodium may be prescribed for patients who are following out-of-province protocols and at the discretion of the physician. The initial adult dose of mycophenolate sodium is 720 mg PO bid. Total daily dose is 1.44 gram [(8)].

ADULT Heart Transplant Recipients
Mycophenolate sodium may be prescribed at the discretion of the physician, in patients who are intolerant of mycophenolate mofetil. The initial adult dose of mycophenolate sodium is 720 mg PO bid. Total daily dose is 1.44 gram [8].

Therapeutic Drug Monitoring

Mycophenolic acid (MPA) blood concentrations are not done routinely at adult transplant centres.

For pediatric transplant recipients, MPA drug level monitoring is routinely done to assess individual patient's drug exposure.

For adult heart transplant patients, although not routinely done, if a patient shows signs MPA gastrointestinal side effects or rejection, a follow up level may be obtained four to eight weeks after the initial level to ensure appropriate dosage.

Target Mycophenolic Acid Blood Concentrations for Heart Transplant Recipients (Nov 2014)

Patient Status	Mycophenolic Acid Trough Blood Concentrations (mg/L) 12 hours Post Dose Tandem Mass Spectrometry Assay*
Stable and no transplant rejection	1.7 to 4
Has transplant rejection	2.5 to 4
Has MPA side effects and is stable	1.7

*Assay done at Vancouver General Hospital Special Chemistry Lab

AVAILABILITY

Mycophenolate mofetil (brand name: CellCept; various generic brands) is available as 250 mg capsules and 500 mg tablets. Mycophenolate mofetil (CellCept® liquid) is available as a powder for oral suspension which must be reconstituted before dispensing. When reconstituted the oral suspension contains 200 mg/mL mycophenolate mofetil [7].

Mycophenolate mofetil capsules and tablets are contained in a blister pack, which should not be opened until the dose is to be administered. Mycophenolate mofetil has demonstrated teratogenic effects in rats and rabbits therefore tablets should not be crushed and capsules should not be opened or crushed. Avoid inhalation or direct contact with skin and mucous membranes of the powder contained in the capsules or suspension [7].

Mycophenolate sodium (brand name: Myfortic®; various generic brands) is available in two strengths of enteric-coated tablets for oral use containing 180 mg mycophenolic acid as mycophenolate sodium and 360 mg mycophenolic acid as mycophenolate sodium. Tablets are provided in blister packs. The tablets are not be crushed or cut [8].

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Prednisone

INTRODUCTION

Prednisone is a synthetic corticosteroid used for its anti-inflammatory and non-specific immunosuppressive effects.

MECHANISM OF ACTION

Prednisone acts by stabilizing the cell wall and suppressing the body's inflammatory response to foreign proteins. Prednisone:

- reduces activity and volume of lymphatic system (lymphocytopenia)
- decreases immunoglobulin concentrations
- decreases passage of immune complexes through basement membranes
- possibly depresses reactivity of tissue to antigen antibody interactions

PHARMACOKINETICS

Prednisone is readily absorbed from the gastrointestinal tract and is bound to plasma proteins. It is primarily metabolized by the liver to inactive metabolites, which are excreted by the kidney.

THERAPEUTIC USE

Prednisone is used in conjunction with other immunosuppressive medications for transplant rejection prophylaxis and treatment.

CONTRAINDICATIONS AND PRECAUTIONS

One large morning dose or alternate day therapy is less likely to suppress the hypothalamic/pituitary axis than divided daily doses.

Blood pressure, weight, serum glucose, and electrolytes should be monitored routinely while patients are on corticosteroids, Patients on prolonged prednisone may require additional steroid coverage during a stressful period (i.e., infection, trauma, surgical procedure). Chronic use of steroids may suppress growth in pediatric and adolescent patients and should be used with caution.

Use with caution in the elderly and patients with: chronic renal failure, peptic ulcers, cirrhosis, psychoses, congestive heart failure, uremia, diabetes mellitus, glaucoma, hypothyroidism, infection, osteoporosis.

ADVERSE DRUG REACTIONS

Prednisone Adverse Drug Reactions

Area of Effect	Adverse Effects
Nervous system	Headache, vertigo, convulsions, paresthesia, psychoses, pseudotumor cerebri
Dermatologic	Impaired wound healing, petechiae, ecchymoses, striae, hyperpigmentation, hirsutism, acne, dermatitis, urticaria, alopecia, brittle hair
Endocrine/ metabolic	Menstrual irregularities, Cushing's syndrome, growth suppression in children, diabetes mellitus, protein catabolism, hyperglycemia, glycosuria, hypernatremia, hypokalemia, hypocalcemia
Gastrointestinal	Nausea, vomiting, increased appetite, weight gain, peptic ulcer, pancreatitis
Neuromuscular	Myopathy, osteoporosis, aseptic necrosis of femoral and humoral heads, spontaneous fractures
Ocular	Posterior subcapsular cataracts, increased intraocular pressure, glaucoma
Other	Hypersensitivity reactions

DRUG INTERACTIONS

Prednisone Drug Interactions

Drug	Effect	Mechanism	Importance
Alcohol, Anti-inflammatory drugs	Enhanced ulcerogenic effect	Additive	Caution
Amphotericin B, Potassium - depleting diuretics	Enhanced potassium depletion	Additive	Caution
ASA	Increased renal excretion of ASA	Unknown	Caution
Barbiturates, Phenytoin, Rifampin	Reduced steroid effect	Increased steroid metabolism	Caution
Digoxin	Increased arrhythmia associated with hypokalemia	Additive	Caution
Isoniazid	Decreased isoniazid plasma levels	Increased hepatic metabolism or renal excretion of Isoniazid	Caution
Insulin or Antidiabetics	Decreased hypoglycemia response	Steroids increase blood glucose	Caution
Oral contraceptives	Increased corticosteroid effect	Decreased Corticosteroid metabolism	Caution
Vaccines	Decreased antibody response	Steroid effect	Caution

DOSE AND ADMINISTRATION

Following transplant, the patient may be prescribed methylprednisolone IV. When the patient can tolerate oral medications, prednisone may be started. Give prednisone with food or milk to reduce gastric irritation.

Adult Kidney Transplant Recipients

The administration of prednisone varies in kidney transplant recipients. Patients may be on one of the following regimens:

Rapid steroid elimination: Prednisone is withdrawn quickly post-transplant over a maximum of 7 days.

Early Steroid Withdrawal: Prednisone is tapered and withdrawn over the first few weeks to months, post-transplant. This approach has risks and the primary transplant center should be contacted as these patients are at high risk for acute rejection.

Late Steroid Withdrawal: Prednisone is withdrawn later than 6 months post-transplant. This is generally unsafe and has little benefit. Therefore patients who have been on steroids for over the first six months post-transplant should continue on prednisone indefinitely. The prednisone maintenance dose should be the lowest possible dose, down to a minimum of 7.5 mg on alternate days or 5 mg daily. Consultation with the transplant nephrologist is highly recommended before steroids are withdrawn.

PEDIATRIC Kidney Transplant Recipients

Pediatric Standard Steroid Taper Immediately Post-Transplant

Days Post Transplant	Pediatric Drug and Dose
Day 1	**MethylpredniSOLONE** 300 mg/m^2 IV ONCE (Maximum 500 mg)
Day 2-7	**PredNISone** 40 mg/m^2 PO daily (Maximum 60 mg daily)
Day 8-14	30 mg/m^2 PO daily (Maximum 45 mg daily)
Day 15-28	20 mg/m^2 PO daily (Maximum 30 mg daily)
Week 5-8	10 mg/m^2 PO daily (Maximum 15 mg daily)
Week 9-12	5 mg/m^2 PO daily (Maximum 7.5 mg daily)
Week 13-16	3 mg/m^2 PO daily (Maximum 5 mg daily)
Week 17 onwards	3 mg/m^2 PO THREE times weekly on MON, WED, FRI (Maximum 5 mg THREE times weekly)

Acute T-Cell Mediated Rejection Protocol: Pediatric Kidney Transplant Recipients
Prednisone Taper

Days of Treatment	Pediatric Drug and Dose
Day 0, 1 and 2	**MethylpredniSOLONE** 300 mg/m^2 IV ONCE daily x 3 doses (Maximum 500 mg per dose)
Day 3-5	**PredNISone** 40 mg/m^2 PO daily (Maximum 60 mg daily)
Day 6-8	20 mg/m^2 PO daily (Maximum 30 mg daily)
Day 9-11	10 mg/m^2 PO daily (Maximum 15 mg daily)
Day 12-14	5 mg/m^2 PO daily (Maximum 7.5 mg daily)
Day 15 onwards	3 mg/m^2 PO daily (Maximum 5 mg daily)

ADULT Liver Transplant Recipients
Prednisone 20 mg (0.3 mg/kg) PO daily is usually begun on day six post - transplant. Dosage is tapered so patient is usually steroid-free by four to six months.

ADULT Lung Transplant Recipients
Methylprednisolone is given for the first 24 hours post - transplant. Prednisone is then begun at a dose of 1 mg/kg/day PO, tapering by 5 mg/day until 15 mg PO daily is reached. Hold dosage at 15 mg PO daily up to six months post – transplant, then decrease to 10 mg PO daily until one year, then, decrease to 5 mg PO daily. Continue prednisone 5mg PO daily indefinitely.

ADULT Heart Transplant Recipients
Methylprednisolone is given for the first 24 hours post-transplant or until the patient is receiving oral intake. Prednisone is then begun at a dose of 0.5 mg/kg/day PO, tapering by 5 mg/day until 20 mg PO daily is reached. If there is no transplant rejection, the goal is to have patients taper off prednisone over the first three to four months post-transplant.

If a patient develops severe transplant rejection methylprednisolone 1 gram IV for 3 days is given, or, if the patient with severe transplant rejection is hemodynamically stable prednisone 100 mg PO daily for 3 days is given. After the three days return to previous prednisone dose, or as prescribed by the physician and then continue to taper

AVAILABILITY

Prednisone is available in oral tablets of 1 mg, 5 mg, and 50 mg strengths. Prednisone is available from several drug manufacturers.

Prednisolone suspension (Pediapred® Sanofi-Aventis Canada Inc.) is available in 1 mg/mL strength and has a pleasant raspberry flavour. Prednisone suspension is prepared at B.C.'s Children's Hospital in 5 mg/mL strength and has a terrible taste.

Sirolimus

INTRODUCTION

Sirolimus is a potent immunosuppressive agent. The pharmacokinetic and drug interaction profile of sirolimus is similar to cyclosporine and tacrolimus, but it has a unique mechanism of action and adverse effect profile [1, 2]. Sirolimus has demonstrated efficacy and safety in two large clinical trials in kidney transplantation when used in combination with cyclosporine and prednisone. Acute rejection episodes were significantly decreased compared with azathioprine or placebo. However, there was no change in graft survival over the first two years post-transplant [3, 4].

MECHANISM OF ACTION

Sirolimus is a macrolide antibiotic, structurally related to tacrolimus, with immunosuppressive, antitumor, and antifungal properties. Sirolimus acts during both co-stimulatory activation and cytokine-driven pathways via a unique mechanism: inhibition of a multifunctional serine-threonine kinase, mammalian target of rapamycin (mTOR). Sirolimus blocks the response of T- and B-cell activation by cytokines, which prevents cell-cycle progression and proliferation. In contrast, tacrolimus and cyclosporine inhibit the production of cytokines [5, 6, 7].

Transplant patients are at particular risk of skin tumors including squamous cell carcinoma, Kaposi sarcoma and the group of post-transplant lymphoproliferative diseases. Preliminary clinical studies have reported a lower incidence of skin malignancy in patients treated with sirolimus compared with cyclosporine at the time of transplantation [8]. Patients receiving sirolimus without cyclosporine or sirolimus maintenance therapy after early cyclosporine withdrawal have lower rates of malignancy in the first 2 years after renal transplantation [9].

PHARMACOKINETICS

Most of the available pharmacokinetic data for sirolimus has been obtained from stable renal transplant patients [1]. Sirolimus appears to exhibit much of the same pharmacokinetic variability that occurs with cyclosporine and tacrolimus.

Following oral administration, sirolimus is rapidly, but poorly, absorbed with peak concentrations occurring at about 0.5 to 2 hours.

The systemic bioavailability is approximately 14% after administration of sirolimus oral solution. The mean bioavailability of sirolimus after administration of the tablet is about 27% higher relative to the oral solution. Sirolimus oral tablets are not bioequivalent to the oral solution in kidney transplant recipients. Fatty meals reduce the maximum concentration (Cmax) of sirolimus obtained and increase the time to peak sirolimus concentration (Tmax).

To minimize variability sirolimus oral solution and tablets should be taken consistently with or without food.

The mean volume of distribution is about 12 L/kg, with approximately 92% plasma protein binding. Sirolimus is metabolized by both cytochrome P450 IIIA4 (CYP3A4) and P-glycoprotein into more than seven metabolites that do not contribute to the immunosuppressive activity. The mean half-life is about 57 to 62 hours. Large inter-patient variability exists in the clearance of sirolimus. Liver disease significantly increases sirolimus bioavailability, reducing its clearance and prolonging its elimination half-life. In renal transplant patients, whole blood trough concentrations are significantly correlated with AUC (r^2=0.96), and trough concentrations of sirolimus appear to be related to the immunosuppressive effects and toxicity of the drug [1, 2, 5, 6, 10].

THERAPEUTIC USE

ADULT and PREDIATRIC Kidney and Kidney-Pancreas Transplant Recipients

Sirolimus is indicated for the prophylaxis of renal transplant rejection in the following patients:

- Patients who were enrolled in a sirolimus clinical trial
- Patients who have developed severe calcineurin inhibitor toxicity (nephrotoxicity or neurotoxicity [11]. Definition of severe nephrotoxicity: Biopsy-proven calcineurin inhibitor nephrotoxicity despite therapeutic concentrations of cyclosporine or tacrolimus. Increase in serum creatinine must be at least 50% above baseline. In this case sirolimus would be used as a substitute for cyclosporine or tacrolimus, in combination with mycophenolate mofetil or azathioprine.
- Patients who have developed severe refractory BK virus-induced nephropathy while on a calcineurin inhibitor. The calcineurin inhibitor would be replaced with sirolimus.
- Patient has recurrent skin cancer or has renal cell cancer [8, 9]. **Prior to beginning sirolimus for cancer indication, the patient must be discussed with the primary transplant centre** to be assessed by dermatology and the renal transplant team.
- For other cancers, sirolimus must be approved by a transplant nephrologist at the patient's primary transplant centre, either Vancouver General Hospital, St. Paul's Hospital or B.C.'s Children's Hospital.
- Refractory rejection in pediatric transplant recipients.

(See Appendix A: BC Transplant Fax Form: Application for Sirolimus in Renal Transplant Recipients) Form is to be completed and sent to BC Transplant from Transplant Clinics.

Liver Transplant Recipients

Sirolimus is only indicated for prophylaxis of liver transplant rejection under special circumstances for the following patients. It is not to be used as first line therapy and should

be used with caution in the first three months post-transplant as its use has been associated with thrombotic events including DVT's [14-19]. **If sirolimus is to be used in a patient, the prescribing physician must discuss the risk/benefit of sirolimus in liver transplantation with the liver team and patient.**

- Patient has developed calcineurin inhibitor nephrotoxicity or neurotoxicity despite calcineurin inhibitor blood concentrations within the therapeutic range.
- Patient has hepatocellular carcinoma, skin or other types of cancers.
- Patient has developed refractory transplant rejection, and not responding to other immunosuppressants
- Patients with intolerance to calcineurin inhibitors that is potentially life threatening or has significant morbidity including hypersensitivity reactions or microangiopathy.

Lung Transplant Recipients

Sirolimus is not indicated for lung transplant recipients. However, in exceptional circumstances on a case- by- case basis sirolimus may be prescribed by the lung transplant physician at Vancouver General Hospital. Sirolimus is not to be given for the first three months after transplant due to the interference with wound healing.

Sirolimus may be considered as a 4th line agent in the following patient situations:

- Recurrent rejection on standard therapy
- Bronchiolitis obliterans syndrome (BOS)
- Renal dysfunction
    - May be added in patients with marginal renal function when higher doses of tacrolimus cannot be used
    - Must check proteinuria, if moderate to high proteinuria do NOT start sirolimus
    - Must follow albumin creatinine ratio
- Add to therapy in patients who cannot tolerate tacrolimus, use in combination with mycophenolate and prednisone
- Lymphangioleiomyomatosis (LAM)

Cardiac Transplant Recipients

Sirolimus is only indicated for prophylaxis of heart transplant rejection in the following patients. It is NOT to be used within the first three months post-transplant

- In addition to a calcineurin inhibitor in patients who have recurrent or persistent transplant rejection within the first year post transplant
- Patient has developed cardiac allograft vasculopathy (CAV)
- Patient has developed calcineurin inhibitor toxicity
- Patient is following an out-of-province protocol
- Patient has developed cancer

(See Appendix B: BC Transplant Fax Form: Application for Sirolimus in Heart Transplant Recipients) Form is to be completed and sent to BC Transplant from Transplant Clinics.

ADVERSE DRUG REACTIONS

Sirolimus exhibits a unique adverse effect profile compared with other immunosuppressive agents. Most adverse effects are dose/concentration dependent. The incidence of adverse reactions was determined in two randomized, double-blind, multi-center controlled trials in which patients received sirolimus or azathioprine or placebo [3, 4]. In the trials all patients received cyclosporine and prednisone.

Adverse reactions associated with the administration of sirolimus that occur at a significantly higher frequency than patients receiving azathioprine or placebo include arthralgia, hirsutism, diarrhea, hypertension, hypokalemia, lymphocele, peripheral edema, rash, tachycardia and some infections. Dose related increases in triglycerides and cholesterol and decreases in platelets and hemoglobin have occurred in patients receiving sirolimus [1, 2, 6, 10, 20, 21].

Sirolimus Adverse Drug Reactions

Area of Affect	Adverse Effect	Lab Results
Common:		
Body (as a whole)	Abdominal pain Asthenia Headache Lymphocele Pain	
Cardiovascular	Hypertension	
Digestive System	Constipation Diarrhea Nausea	
Hematologic (bone marrow suppression)	Anemia Leukopenia Thrombocytopenia	Decreased HgB Decreased WBC Decreased platelets
Hepatic	Hepatic artery thrombosis (HAT)***	Increased LFTs Leucocytosis High fever Positive blood cultures
Infectious	Increased risk**	
Metabolic	Hypercholesterolemia Hyperlipidemia* (50% of patients) Peripheral Edema	Increased cholesterol Increased triglycerides

Sirolimus Adverse Drug Reactions Cont.

Area of Affect	Adverse Effect	Lab Results
Skin/mucous membranes	Oral ulceration Acne Rash Bronchial anastomotic dehiscence	
Respiratory	Interstitial Pneumonitis** Upper respiratory infections	
CNS	Insomnia	
Rare:		
Lymphoma	Increased risk	
Nephrotoxicity	Increased risk in combination with Cyclosporine	Increased Serum Creatinine Increased Urea

* **Hyperlipidemia** is a major complication of sirolimus therapy. In Phase III trials, treatment of new onset hyperlipidemia was reported in 42 to 52% of patients treated with sirolimus. All patients receiving sirolimus should be closely monitored for hyperlipidemia and treated as required for any unexplained muscle weakness or pain, especially if associated with malaise or fever. Patients treated with a statin should be made aware of and monitored for rhabdomyolysis [1, 22].

** **Antimicrobial prophylaxis against PCP** for 12 months and **CMV antiviral prophylaxis** is essential [23].

*** **Hepatic artery thrombosis** (HAT) is a clinical diagnosis, which depends on a strong index of suspicion. An angiogram is the only specific test, which can confirm that the hepatic artery is not patent [24].

DRUG INTERACTIONS

Sirolimus like tacrolimus and cyclosporine is metabolized by the cytochrome P450 3A4 enzyme system. Therefore medications known to affect this system will likely alter sirolimus metabolism, resulting in changes to sirolimus blood concentrations.

Important Drug Interactions of Cyclosporine (CSA), Tacrolimus (TAC) and Sirolimus

(Prepared by Nilu Partovi, Clinical Pharmacy Specialist, Vancouver General Hospital, November 2008)

The table outlines major drug interactions only, and is not all-inclusive. The majority of interactions are the result of effects on the cytochrome P450 3A4 enzyme. Medications included below should be avoided when an appropriate alternative exists. If no alternatives are available, please advise the transplant clinic so that appropriate blood work can be arranged or advised. For a complete list of drug interactions, refer to tertiary references.

Drug A) Drugs that **DECREASE** CSA/TAC/ Sirolimus levels	**Possible Mechanism / Onset and severity**	**Adverse Effects**	**Management**
Anticonvulsants: ▪ phenytoin ▪ carbamazepine ▪ phenobarbital, primidone	Enzyme induction ↑ CSA/TAC/sirolimus metabolism • Delayed / major • Delayed/ moderate • Delayed / major	↓ effectiveness of CSA/TAC/sirolimus which may lead to rejection	↑ CSA/TAC/sirolimus dose by 30% and monitor levels following addition, dose change or discontinuation.
Antimicrobial: ▪ rifampin ▪ caspofungin **(Tacrolimus ONLY)**	Induction of hepatic enzymes • Delayed / Major Mechanism is unknown • Delayed/ moderate	Same as above	Monitor CSA/TAC/sirolimus levels following addition, dose change or discontinuation. Monitor tacrolimus level closely when caspofungin is initiated or dose changes and when caspofungin discontinued.

Important Drug Interactions of Cyclosporine (CSA), Tacrolimus (TAC) and Sirolimus cont.

(Prepared by Nilu Partovi, Clinical Pharmacy Specialist, Vancouver General Hospital, November 2008)

B) Drugs that **INCREASE** CSA/TAC/ Sirolimus levels			
Antimicrobial: ▪ erythromycin, clarithromycin (Biaxin) ▪ Azole Antifungals (fluconazole, ketoconazole, itraconazole, posaconazole, voriconazole)	↓ CSA/TAC/sirolimus metabolism, ↑ rate of absorption, ↓volume of distribution • Delayed / major ↓CSA/TAC/sirolimus metabolism • Delayed/ moderate	↑ CSA/TAC/sirolimus levels, ↑ risk of toxicity	Monitor CSA/TAC/sirolimus levels following addition, dose change or discontinuation. Monitor serum creatinine
Antidepressants: fluoxetine, fluvoxamine greater than sertraline, venlafaxine, mirtazapine, paroxetine	↓ CSA/TAC/sirolimus metabolism • Delayed/ moderate	↑ CSA/TAC/sirolimus levels, ↑ risk of toxicity	Consider another antidepressant (citalopram, escitalopram) and/or monitor CSA/TAC/sirolimus levels closely
Cardiovascular: ▪ diltiazem, verapamil ▪ amiodarone	May inhibit hepatic metabolism of CSA/TAC/sirolimus • Delayed / Major	↑CSA/TAC/sirolimus levels, ↑ risk of toxicity	Monitor CSA/TAC/sirolimus levels following addition, dose change or discontinuation.

Pharmacodynamic Interactions of Cyclosporine (CSA), Tacrolimus (TAC) and Sirolimus

(Prepared by Nilu Partovi, Clinical Pharmacy Specialist, Vancouver General Hospital, November 2008)

Drug	Proposed Mechanism and Possible effects	Management
aminoglycosides, amphotericin B, NSAIDS, C0X-2 inhibitors **(CSA and tacrolimus ONLY)**	Additive nephrotoxicity	These drugs should be avoided in transplant recipients due to increased nephrotoxicity. The only exception is when the benefit clearly outweighs the potential risks and only used for short-term treatment. Renal function should be monitored closely while these drugs are used with cyclosporine or tacrolimus.
HMG-CoA Reductase Inhibitors: Example: lovastatin, simvastatin, Atorvastatin	CSA/TAC/sirolimus may ↓ metabolism of these agents →accumulation of statin and toxicity Myalgia, myopathy, rhabdomyolysis	Start with low dose of these agents and monitor very closely for toxicity
digoxin	↓ volume of distribution of digoxin by 50-70%, ↑ digoxin half-life by 30-40%, and increased digoxin levels Digoxin toxicity such as vomiting, cardiac arrhythmia's	Initiate low dose and follow up with serum digoxin levels Closely monitor for symptoms of digoxin toxicity
nifedipine phenytoin **(cyclosporine ONLY)**	Additive incidence of gingival hyperplasia with CSA (not tacrolimus) Incidence increases from 8% (CSA alone) to 51% (combination)	Avoid long term use if possible. Good dental/oral hygiene with regular dentist visits

DOSE AND ADMINISTRATION

ADULT Kidney and Kidney-Pancreas Transplant Recipients
Prior to beginning sirolimus, the primary transplant centre must be consulted due to the high rate of sirolimus toxicity. Caution is advised for patients on steroid free protocols.

When sirolimus is used in a patient with recurrent skin cancer or renal cell cancer, the patient **must be discussed with** the primary transplant centre before initiating sirolimus therapy. The patient will be assessed by both the dermatology and renal transplant teams. At the time sirolimus therapy is begun, other immunosuppressive therapy will be evaluated [25]. Sirolimus is not to be used in *de novo* adult renal transplant recipients, nor is a loading dose administered. Most centres will overlap the current immunosuppressants until their sirolimus levels is at therapeutic levels. This can take 2-3 weeks due to its long pharmacokinetic half-life.

The initial oral maintenance dose of sirolimus is 2 to 5 mg daily. Subsequent doses are based on the achievement of therapeutic trough concentrations [1].

PEDIATRIC Kidney Transplant Recipients
Children (13 years old and older, and body weight less than 40 kg): Sirolimus loading dose is 3 mg/m^2 PO for 1 dose. Initial maintenance dose is 1 mg/m^2/day PO divided every twelve hours or once daily. Adjust dose to achieve target sirolimus blood concentration.

Pediatric patients with body weight greater than 40 kg: Loading dose is 6 mg PO for 1 dose and then maintenance dose 2 mg PO once daily. Adjust dose to achieve target sirolimus blood concentration.

NOTE: For patients who are converting from another immunosuppressant, the loading dose may be omitted.

ADULT Liver Transplant Recipients
The use of sirolimus is not recommended to be used within the first three months post liver transplant due to an increased risk of thrombotic events including hepatic artery thrombosis and delayed wound healing. The safety and efficacy of sirolimus has not been established in liver transplant recipients. The risk/benefit ratio of sirolimus in any liver transplant recipient must be discussed with patient.

When sirolimus is used in combination with mycophenolate mofetil or azathioprine and corticosteroids for maintenance therapy in liver transplant recipients, a sirolimus dosage of 2 to 3 mg PO daily (0.05 mg/kg/day) is prescribed and then dosage is adjusted to achieve therapeutic target concentrations [14-19].

ADULT Heart Transplant Recipients
Sirolimus is not to be used within the first three months post- heart transplant. Sirolimus dosages are adjusted based on sirolimus blood concentrations.

ADULT Lung Transplant Recipients
Sirolimus may be used in exceptional circumstances on a case by case basis when prescribed by the transplant physician.

Administration
Sirolimus should be taken consistently either with or without food [1,2,10]. Cyclosporine increases absorption of sirolimus, and their administration should be separated by four hours (sirolimus should be taken four hours after the cyclosporine dose). Concomitant administration may increase the risk of sirolimus-associated adverse effects [1, 2, 6]. However, the combination of sirolimus and tacrolimus can be taken at the same time.

The dose of sirolimus solution should be added to at least 60 mL of water or orange juice in a glass or plastic container (not a Styrofoam or paper container), stirred vigorously and drunk at once. Grapefruit juice should be avoided since it can unpredictably alter sirolimus pharmacokinetics. The sirolimus container should be rinsed with an additional volume of 120 mL of water or orange juice, stirred vigorously, and drunk at once [1,2,10,22]. Swish mouth with water and spit after liquid or if split tablets are given, to help reduce mouth sores.

Monitoring
It is recommended that blood sirolimus trough blood concentrations be monitored in all patients, with particular attention to the following patient groups [23]:

- Pediatric patients
- Patients greater than and equal to 13 years old and weighing less than 40 kg
- Patients with significant liver disease
- Patients receiving medications that inhibit Cytochrome P_{450} 3A4 or P-glycoprotein (i.e. diltiazem, ketoconazole, fluconazole, verapamil) or induce Cytochrome P_{450} 3A4 (rifampin, phenytoin, carbamazepine)
- Patients whose cyclosporine or tacrolimus dose has been markedly reduced or discontinued
- Patients receiving sirolimus plus low-dose tacrolimus
- Patients who are at high risk for acute rejection
- Patients whom are on sirolimus monotherapy

Sirolimus serum concentrations are to be obtained once weekly until therapeutic range is achieved and then monthly.

The high performance liquid chromatography - tandem mass spectrometry assay (HPLC-TMS) to determine sirolimus concentrations is only done at Vancouver General Hospital and Victoria General Hospital. Samples must be sent to Vancouver General Hospital or Victoria General Hospital for analysis.

Target Sirolimus Whole - Blood Concentrations for Transplant Recipients

Table 1: Renal Transplants

Time Post Transplant (Months)	Sirolimus Trough Concentration (ng/mL)* (When sirolimus is used with mycophenolic acid and steroids)	Sirolimus Trough Concentration (ng/mL)* (When sirolimus is used as a single agent +/- steroids)
ADULT Kidney Transplants (May 2017)		
Greater than 3 months	5 to 10	8 to 10
PEDIATRIC Kidney Transplants (May 2017)		
Greater than 3 months	4 to 6	Not used as a single agent at B.C.'s Children's Hospital

*Tandem Mass Spectrometry Assay

Table 2 Liver, Lung and Heart Transplants

Time Post Transplant (Months)	Sirolimus Trough Concentration (ng/mL)* (When sirolimus is used with tacrolimus or cyclosporine +/- mycophenolic acid and steroids)	Sirolimus Trough Concentration (ng/mL)* (When sirolimus is used as a single agent +/- steroids)
ADULT Liver Transplants (May 2021)		
1 to 3 months	8 to 12	10 to 15
Greater than 3 months	5 to 10	8 to 12
ADULT Lung Transplants (Dec 2020)		
contact lung transplant clinic for patient specific targets		
ADULT Heart Transplants (Nov 2014)		
All	4 to 8	8 to 12

*Tandem Mass Spectrometry Assay

AVAILABILITY

Sirolimus (Rapamune® Pfizer) is available for oral administration both in solution and tablet formulations. It is supplied as oral solution at a concentration of 1 mg/mL in glass bottles of 60 mL and as a 1 mg white triangular tablet. Solutions should be stored in the refrigerator and protected from light [(1)]. Once opened the solution should be used within one month.

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Tacrolimus: IMMEDIATE Release and EXTENDED Release

INTRODUCTION

Tacrolimus is an immunosuppressant used in combination with other immunosuppressants to prevent transplant rejection.

In BC, tacrolimus is available in FOUR different formulations **(non-interchangeable formulations**):

- Tacrolimus IMMEDIATE release (**Sandoz tacrolimus** or **Prograf® tacrolimus)** a twice daily formulation.
- Tacrolimus EXTENDED release (**Advagraf® tacrolimus or Envarsus PA® tacrolimus)** a once a day formulation.

MECHANISM OF ACTION

The mechanism of action of tacrolimus is similar to that of cyclosporine, even though their chemical structures differ greatly. Tacrolimus inhibits T-lymphocyte activation, although the exact mechanism is not known. Experimental evidence suggests tacrolimus becomes activated only when complexes with intracellular receptors or cytosine binding proteins known as immunophilins. The immunophilin - drug complex binds competitively to and inhibits calcineurin. Inhibition of calcineurin inhibits transcription, is believed to mediate the immunosuppressive activity of both tacrolimus and cyclosporine [(1)].

PHARMACOKINETICS

Tacrolimus is a hydophobic molecule with poor absorption from the gastrointestinal tract. The oral bioavailability of tacrolimus ranges from 5 to 67%, with a mean bioavailability of 29% in patients who have undergone liver, small bowel, or kidney transplantation. The presence of food reduces the absorption of tacrolimus. Maximum absorption occurs when the medication is taken on an empty stomach. Bile does not appear to influence tacrolimus absorption.

Tacrolimus is highly lipophilic and undergoes extensive tissue distribution, as evidenced by its large volume of distribution (V_{ss} in plasma ranges from 5.6 to 65 L) [(1, 2)].

Tacrolimus EXTENDED release a once a day formulation has prolonged release characteristics [(2)]. There is a marked reduction of intra-subject variability for exposure (AUC 0-24) in black kidney transplant recipients at steady state after converting from tacrolimus IMMEDIATE release (% CV 25.4% to tacrolimus EXTENDED release (% CV 12.2%). In white kidney transplant

recipients the intra-subject variability for exposure at steady state was similar after converting from tacrolimus, IMMEDIATE release (% CV 12.2%) to tacrolimus EXTENDED release (14.1%). Black patients require higher tacrolimus EXTENDED release doses to attain comparable trough concentrations compared to white patients [(2)].

Tacrolimus is extensively metabolized primarily by the hepatic P_{450} enzyme system. Less than one percent of the administered dose is excreted unchanged in urine, bile, and feces [(1)].

Pediatric transplant patients appear to eliminate tacrolimus from the body more rapidly than do adult transplant patients on a body-weight basis. Therefore, pediatric patients often require higher doses of tacrolimus based on mg/kg body weight than do adults to maintain similar plasma tacrolimus concentrations. Elimination half-life from whole blood is approximately 12 hours in adult liver transplant patients and 21 hours in healthy adult volunteers.

THERAPEUTIC USE

Tacrolimus IMMEDIATE release is indicated for prophylaxis and treatment of rejection following renal, liver, heart, lung and pancreas transplantation when used in combination with other immunosuppressants.[(1)].

Tacrolimus may be used in adults, pre-transplant in combination with mycophenolate mofetil, plasma exchange and rituximab for ABO incompatible recipients who may receive a living donor kidney transplant.

Tacrolimus may be used in pediatric patients pre-transplant in combination with mycophenolate mofetil for recipients who may receive a living donor transplant.

It is important to note several international safety alerts have been sent out regarding prescribing, dispensing and administration errors of tacrolimus EXTENDED release.

Tacrolimus IMMEDIATE release and tacrolimus EXTENDED release **are not interchangeable** and should not be substituted without careful therapeutic monitoring as both have a very narrow therapeutic index. Tacrolimus IMMEDIATE release is dosed every 12 hours and tacrolimus EXTENDED release is dosed every 24 hours. Care must be taken when converting a patient from tacrolimus IMMEDIATE release to tacrolimus EXTENDED release.

Patients and health care providers must understand the once a day dosage regimen and which drug formulation (ie brand name) they are receiving as they are not interchangeable. Clinicians (providers) must always specify which brand name (eg. Sandoz tacrolimus, Prograf tacrolimus, Advagraf tacrolimus, Envarsus PA tacrolimus) is being prescribed. Any changes in brand and dose should done under the close supervision of the patient's transplant team [4-7].

ADVERSE DRUG REACTIONS

Adverse effects experienced by patients receiving tacrolimus are similar to those experienced by patients receiving cyclosporine. The principal adverse effects of tacrolimus are tremor, headache, nausea, diarrhea, hypertension, and renal impairment. Adverse reactions experienced by patients receiving with tacrolimus EXTENDED release are comparable to those patients receiving tacrolimus IMMEDIATE release [2].

Anaphylactic reactions have been reported in animals and humans following intravenous administration, most likely due to the polyoxyl-60-hydrogenated castor oil vehicle. All patients should be carefully observed for evidence of possible hypersensitivity and medications for the treatment of anaphylaxis must be available at the bedside.

Tacrolimus Adverse Drug Reactions

Area of Affect	Side Effect	Lab Results
Nervous system	Headache Tremor Insomnia Paresthesia	
Gastrointestinal	Diarrhea Nausea Constipation LFT abnormal Anorexia Vomiting	Increased liver function tests
Cardiac	Hypertension	
Dermatologic	Pruritis Rash Alopecia	
Endocrine	Hyperglycemia	Increased serum glucose
Hematologic	Lymphoproliferative diseases Anemia Leukocytosis Thrombocytopenia	Decreased hemoglobin Decreased WBC Decreased platelets
Infectious	CMV	
Musculoskeletal	Abdominal pain Pain Fever Asthenia Back pain Ascites	
Renal	Nephrotoxicity	Increased serum creatinine

DRUG INTERACTIONS

Tacrolimus, sirolimus and cyclosporine are metabolized primarily by the hepatic P450 system. Therefore, medications known to affect cyclosporine and sirolimus metabolism are also likely to alter tacrolimus metabolism, resulting in changes in tacrolimus blood concentrations.

Important Drug Interactions of Cyclosporine (CSA), Tacrolimus (TAC), and Sirolimus

(Prepared by Nilu Partovi, Clinical Pharmacy Specialist, Vancouver General Hospital, November 2008)

The table outlines major drug interactions only, and is not all-inclusive. The majority of interactions are the result of effects on the cytochrome P450 3A4 enzyme. Medications included should be avoided when an appropriate alternative exists. If no alternatives are available, please advise the transplant clinic so that appropriate blood work can be arranged or advised. For a complete list of drug interactions, refer to tertiary references.

Drug A) Drugs that **DECREASE** CSA/TAC/ Sirolimus levels	**Possible Mechanism / Onset and severity**	**Adverse Effects**	**Management**
Anticonvulsants: ▪ phenytoin ▪ carbamazepine ▪ phenobarbital, primidone	Enzyme induction ↑ CSA/TAC/sirolimus metabolism • Delayed / major • Delayed/ moderate • Delayed / major	↓ effectiveness of CSA/TAC/sirolimus which may lead to rejection	↑ CSA/TAC/sirolimus dose by 30% and monitor levels following addition, dose change or discontinuation.
Antimicrobial: ▪ rifampin ▪ caspofungin **(Tacrolimus ONLY)**	Induction of hepatic enzymes • Delayed / Major Mechanism is unknown • Delayed/ moderate	Same as above	Monitor CSA/TAC/sirolimus levels following addition, dose change or discontinuation. Monitor tacrolimus level closely when caspofungin is initiated or dose changes and when caspofungin discontinued.

B) Drugs that **INCREASE** CSA/TAC/ Sirolimus levels			
Antimicrobial: ▪ erythromycin, clarithromycin (Biaxin) ▪ Azole Antifungals (fluconazole, ketoconazole, itraconazole, posaconazole, voriconazole)	↓ CSA/TAC/sirolimus metabolism, ↑ rate of absorption, ↓volume of distribution • Delayed / major ↓CSA/TAC/sirolimus metabolism • Delayed/ moderate	↑ CSA/TAC/sirolimus levels, ↑ risk of toxicity	Monitor CSA/TAC/sirolimus levels following addition, dose change or discontinuation. Monitor serum creatinine
Antidepressants: fluoxetine, fluvozamine >> sertraline, venlafaxine, mirtazapine, paroxetine	↓ CSA/TAC/sirolimus metabolism • Delayed/ moderate	↑ CSA/TAC/sirolimus levels, ↑ risk of toxicity	Consider another antidepressant (citalopram, escitalopram) and/or monitor CSA/TAC/sirolimus levels closely
Cardiovascular: ▪ diltiazem, verapamil ▪ amiodarone	May inhibit hepatic metabolism of CSA/TAC/sirolimus • Delayed / Major	↑CSA/TAC/sirolimus levels, ↑ risk of toxicity	Monitor CSA/TAC/sirolimus levels following addition, dose change or discontinuation.

Pharmacodynamic Interactions of CSA/TAC/ Sirolimus

Drug	Proposed Mechanism and Possible effects	Management
aminoglycosides, amphotericin B, NSAIDS, C0X-2 inhibitors **(CSA and tacrolimus ONLY)**	Additive nephrotoxicity	These drugs should be avoided in transplant recipients due to increased nephrotoxicity. The only exception is when the benefit clearly outweighs the potential risks and only used for short-term treatment. Renal function should be monitored closely while these drugs are used with cyclosporine or tacrolimus.
HMG-CoA Reductase Inhibitors: Example: lovastatin, simvastatin, atorvastatin	CSA/TAC/sirolimus may ↓ metabolism of these agents →accumulation of statin and toxicity Myalgia, myopathy, rhabdomyolysis	Start with low dose of these agents and monitor very closely for toxicity
Digoxin	↓ volume of distribution of digoxin by 50-70%, ↑ digoxin half-life by 30-40%, and increased digoxin levels Digoxin toxicity such as vomiting, cardiac arrhythmia's	Initiate low dose and follow up with serum digoxin levels Closely monitor for symptoms of digoxin toxicity
nifedipine phenytoin **(cyclosporine ONLY)**	Additive incidence of gingival hyperplasia with CSA (not tacrolimus) Incidence increases from 8% (CSA alone) to 51% (combination)	Avoid long term use if possible. Good dental/oral hygiene with regular dentist visits

DOSE AND ADMINISTRATION

Tacrolimus IMMEDIATE release (PROgraf® or Sandoz tacrolimus) is the standard tacrolimus product used in BC Transplant protocols.

ADULT Kidney and Kidney-Pancreas Transplant Recipients

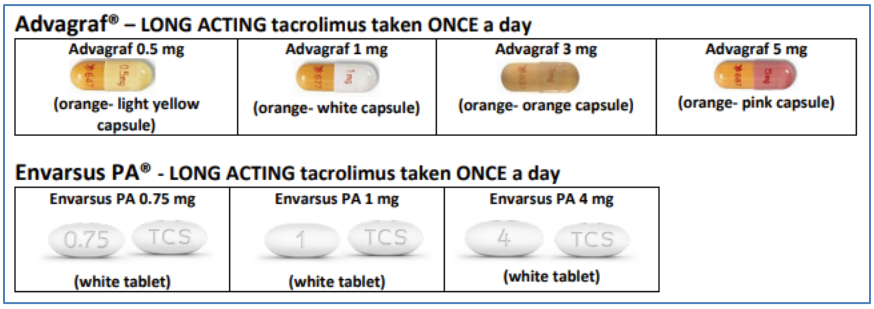
The post-transplant initial adult oral dose of tacrolimus IMMEDIATE release is 0.12 to 0.15 mg/kg/day divided every 12 hours.

The pre-transplant adult dose of tacrolimus IMMEDIATE release is 0.15 mg/kg/day PO divided every 12 hours for 14 days. This is for ABO incompatible recipients who can receive a living donor transplant.

If IV tacrolimus is required it should be given at ¼ total daily adult oral dose (divided BID) over 4 hours or 1/3rd of total daily adult oral dose once a day IV over 3 to 4 hours. Alternatively it may be given as a continuous 24 hour infusion.

Tacrolimus EXTENDED release may be prescribed on a case-by-case basis at the discretion of the transplant physician/pharmacist in patients in whom once daily dosing would be beneficial. BC Transplant has **2 non-interchangeable** formulations of EXTENDED release tacrolimus available:

- Advagraf tacrolimus 0.5 mg, 1 mg, 3 mg and 5 mg capsules – manufacturer Astellas
- Envarsus PA tacrolimus 0.75 mg, 1 mg and 4 mg tablets – manufacturer Paladin/Endo Ventures



Patients converting from tacrolimus IMMEDIATE release to tacrolimus EXTENDED release should be administered a single morning dose of tacrolimus EXTENDED release equivalent to patients' previous stable total daily dose of tacrolimus IMMEDIATE release. Initial conversion ratio:

- Immediate release tacrolimus to Advagraf tacrolimus: **1 mg: 1.2 mg basis***
- Immediate release tacrolimus to Envarsus PA tacrolimus: **1 mg: 0.7 mg basis***

***NOTE:** Recommend consultation with transplant centre clinical pharmacist for conversion protocol.

Subsequent tacrolimus EXTENDED release (Advagraf or Envarsus PA) dosages should be adjusted in order to maintain trough concentrations similar to those prior to conversion [2]. Data indicates de novo black kidney transplant recipients require higher tacrolimus EXTENDED release dosages to attain comparable trough concentrations to Caucasian patients [2].

For patients requiring a switch from tacrolimus to cyclosporine, an estimated conversion of 1:40 (tacrolimus dose to cyclosporine) can be used a starting point.

PEDIATRIC Kidney Transplant Recipients

The initial post-transplant pediatric oral dose of tacrolimus IMMEDIATE release is as follows:

- Children **<12 years:** 0.2 mg/kg/dose every 12 hours
- Children **≥12 years**: 0.1 mg/kg/dose every 12 hours

The post-transplant pediatric IV dose of tacrolimus is 0.03 to 0.15 mg/kg/24 hours via continuous IV infusion (preferred) or given over 4 to 8 hours (higher risk of adverse effects). To switch from intravenous dose to oral dose: multiply IV dose by 3.

For recipients who can receive a living donor transplant, a pre-transplant pediatric dose of tacrolimus IMMEDIATE release (<12yrs: 0.2mg/kg/dose orally every 12 hours, or ≥12yrs: 0.1 mg/kg/dose orally every 12 hours) can be given for up to 14 days before transplant date.

For pediatric patients, when converting between immediate release tacrolimus to an extended release formulation (Prograf/Sandoz tacrolimus to Advagraf), the ratio is usually 1:1.2[8]. Tacrolimus pre-dose levels to be monitored to ensure target range is maintained. There is no data currently on using Envarsus PA tacrolimus in pediatric patients.

ADULT Liver Transplant Recipients

The initial adult oral dose of tacrolimus IMMEDIATE release is 0.03 mg/kg/dose given every 12 hours (approximately 1 mg PO bid) for the first few days post-transplant. This dose helps to ensure the patient does not experience tacrolimus toxicity in case the medication is not being metabolized efficiently. Further dosages are based on therapeutic blood concentrations.

Tacrolimus EXTENDED release may be considered on a case-by-case basis for patients with stable immunosuppression in whom once daily administration would be beneficial as a late change for tacrolimus IMMEDIATE release. Patients converting from tacrolimus IMMEDIATE release to tacrolimus EXTENDED release should be administered a single morning dose of tacrolimus EXTENDED release equivalent to patient's previous stable total daily dosage of tacrolimus IMMEDIATE release on a 1 mg:1 mg basis. Subsequent tacrolimus EXTENDED release doses should be adjusted in order to maintain trough concentrations similar to those prior to conversion [2].

ADULT Lung Transplant Recipients
The adult oral dose of tacrolimus IMMEDIATE release is 0.03 to 0.05 mg/kg/dose PO/NG every twelve hours. Adjust dose if patient is on interacting medications (i.e., fluconazole).

IV tacrolimus is generally not recommended, however if IV tacrolimus is to be used ¼ total daily adult oral dose per day (divided BID) is to be given IV over 4 hours or 1/3rd of total daily adult oral dose once a day IV over 3 to 4 hours.

ADULT Heart Transplant Recipients
The initial adult oral dose of tacrolimus IMMEDIATE release is 0.1 mg/kg/day divided every twelve hours. Dosage is based on tacrolimus blood concentrations.
Therapeutic Drug Monitoring

In British Columbia the assay used for the determination of tacrolimus blood concentrations is a tandem mass spectrometry assay. The assay is done at Vancouver General, St. Paul's and Victoria General Hospitals and LifeLabs. Other hospitals send their tacrolimus blood concentrations to Vancouver General Hospital.

Target Tacrolimus Blood Concentrations for Solid Organ Transplant Recipients

Time Post-Transplant (Months)	Tacrolimus Trough Blood Concentration (ng/mL) 12 hours Post-Dose Tandem Mass Spectrometry Assay	
ADULT Kidney and Kidney/Pancreas Transplants (May 2020)		
Month 1	9 to 12	
Month 2 and 3	8 to 10	
Month 4, 5 and 6	6 to 8	
After 6 months	5 to 7	
PEDIATRIC Kidney Transplants (Oct 2019)		
Month 1	10 to 15	
Month 2 and 3	8 to 12	
Month 4, 5 and 6	6 to 10	
After Month 6	5 to 8	
ADULT Liver Transplants* (May 2021) **Please contact Vancouver General Hospital Transplant Clinic if you have any questions.**		
	Standard Dosing	**Low Target/Kidney Sparing**
Dosing	0.05 mg/kg PO BID	0.03 mg/kg PO BID with basiliximab induction
Less than 1 month	8 to 10	6 to 8
1 to 3 months	7 to 9	6
Greater than 3 months	6 to 8	4 to 6
Greater than 12 months	4 to 6	3 to 5
ADULT Lung Transplants (Dec 2020)		
0 to 6 months	10 to 12	
6 to 12 months	8 to 10	
Greater than 12 months	6 to 8	
*For severe AKI or temporary dialysis with hopes of renal recovery contact transplant clinic for tacrolimus target		
ADULT Heart Transplants (Nov 2014)		
Less than 3 months	9 to 12	
3 to 6 months	8 to 9	
6 to 12 months	6 to 8	
Greater than 12 months	4 to 8	
PEDIATRIC Heart Transplants (Dec 2020)		
0 to 6 months	10 to 12	
6 to 12	8 to 10	
Year 2 and 3	6 to 8	
>3 years (No rejection)	4 to 6	

AVAILABILITY

- Tacrolimus IMMEDIATE release (**PROgraf® tacrolimus or Sandoz tacrolimus**) is available a 0.5 mg, 1 mg and 5 mg capsules.
- Tacrolimus EXTENDED release (**ADVAgraf® tacrolimus,** Astellas) is available as 0.5 mg, 1 mg, 3mg, and 5 mg capsules.
- Tacrolimus EXTENDED release **(Envarsus PA tacrolimus**, Paladin/Endo Ventures) is available as 0.75 mg, 1 mg and 4 mg tablets.

No oral liquid dosage formulation is commercially available. In British Columbia pharmacies dispensing tacrolimus suspension prepare a 1 mg/mL suspension [7]. Contact B.C's Children's Hospital Pharmacy at 604-875 -2059 for suspension preparation instructions.

Tacrolimus is supplied in ampules containing 5 mg tacrolimus IMMEDIATE release (PROgraf® Astellas) per mL for intravenous administration. The intravenous route should only be used if the patient is not able to tolerate oral tacrolimus [1].

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Valganciclovir

INTRODUCTION

Valganciclovir hydrochloride is the salt of the L-valyl ester of Ganciclovir, which is a synthetic 2'-deoxy-guanosine analogue used for the prevention and treatment of cytomegalovirus (CMV) infections in immuno-compromised or immunosuppressed patients [1,2].

MECHANISM OF ACTION

Valganciclovir is a prodrug of ganciclovir. Following oral administration, Valganciclovir is rapidly converted to ganciclovir by intestinal and hepatic esterases. Ganciclovir inhibits replication of herpes viruses and *in vitro* and *in vivo*. The virustatic activity of ganciclovir against CMV is due to the inhibition of viral DNA synthesis [1, 2].

PHARMACOKINETICS

Most reports of the pharmacokinetics of valganciclovir have been in HIV/CMV seropositive and HIV positive patients with CMV retinitis [1-3].

Following oral administration, valganciclovir is rapidly hydrolyzed to ganciclovir by esterases in the intestinal and hepatic cells. After administration of valganciclovir, ganciclovir bioavailability was 60% when taken with food. The bioavailability of valganciclovir is significantly higher than oral ganciclovir. When taken with food steady state ganciclovir AUC increased by 30% and the Cmax increased by 14%, without any change in the time to peak plasma concentrations (Tmax). When taken with food, a 900 mg dose of valganciclovir is essentially equivalent to an IV ganciclovir dose of 5 mg/kg [1,2].

Time to maximum serum ganciclovir concentration (C_{max}) is approximately 2 hours. The C_{max} following administration of 900 mg of valganciclovir to adult patients with normal renal function is 5.6 mcg/mL and the serum concentration at 12 hours after the dose is approximately 1 mcg/mL. In vitro CMV resistance is defined as an IC_{50} greater than and equal to 1.5 mcg/mL. The plasma protein binding of ganciclovir is 2% and less, and has a volume of distribution of approximately 0.7 L/kg. Binding of ganciclovir to plasma proteins is about 1% to 2% [1-3]. Liver transplant recipients attained similar exposures to ganciclovir following the administration of 900 mg of valganciclovir and 5 mg/kg IV ganciclovir [4].

Valganciclovir is eliminated as ganciclovir in the urine via glomerular filtration and active tubular secretion. The renal clearance of ganciclovir is approximately 3 mL/min/kg [1-3].

Ganciclovir clearance is correlated with creatinine clearance. The elimination half-life of ganciclovir is about 4 hours in patients with a creatinine clearance of 75 mL/min and approximately 24 hours in patients with a creatinine clearance between 10 and 20 mL/min [1, 3, 5].

THERAPEUTIC USE

Valganciclovir is approved for the prevention of cytomegalovirus (CMV) disease in solid organ transplant recipients who are at risk.

CONTRAINDICATIONS

Valganciclovir is contraindicated in patients with:

- Absolute neutrophil count less than 500 cells/microliter
- Platelet count less than 25,000 platelets/microliter
- Hemoglobin concentration less than 8 g/L [(1)]

ADVERSE DRUG REACTIONS

Valganciclovir is a prodrug of Ganciclovir, which is rapidly converted to ganciclovir after oral administration. The adverse effects associated with ganciclovir use can therefore be expected to occur with valganciclovir. All of the adverse effects observed in valganciclovir studies have been previously observed with ganciclovir [(1, 2)].

Valganciclovir Adverse Drug Reactions

Area of Effect	Adverse Effects
Gastrointestinal	Diarrhea, nausea, vomiting, abdominal pain, oral candidiasis
Hematologic	Neutropenia, anemia, thrombocytopenia
Body	Fever, headache, fatigue
CNS	Insomnia, paresthesia, peripheral, neuropathy, dizziness
Eye	Retinal detachment
Other	Sinusitis

In animal studies and *in vitro,* ganciclovir has been shown to be carcinogenic, teratogenic, mutagenic and has caused aspermatogenesis. Ganciclovir should be considered a potential teratogen and carcinogen in humans. Women of childbearing potential should be advised that ganciclovir causes birth defects in animals and should not be used during pregnancy. Due to the potential for serious adverse events in nursing infants, mothers should be instructed not to breast feed if they are receiving valganciclovir. Women and men of childbearing potential should be advised to use effective contraception (men–barrier contraception) during treatment with valganciclovir [(1)].

Valganciclovir should be used in caution in patients with renal failure and the dose should be adjusted based on the estimated creatinine clearance [(5)].

DRUG INTERACTIONS

Valganciclovir is a prodrug of ganciclovir, which is rapidly converted to ganciclovir after oral administration. The adverse effects associated with ganciclovir use can therefore be expected to occur with valganciclovir.

Probenicid and other medications secreted by renal organic anion transport system are likely to reduce ganciclovir clearance, causing ganciclovir accumulation, increasing the risk of ganciclovir toxicity.

Co-administration with other myelosuppressive agents (mycophenolic acids, azathioprine) increases the risk of toxicity.

Seizures have been reported in patients taking ganciclovir and imipenem-cilastain concomitantly. This combination should be avoided [(1)].

DOSE AND ADMINISTRATION

The valganciclovir dose depends on patient's renal function, white blood cell count and whether or not the patient is receiving valganciclovir for CMV prophylaxis, pre-emptive treatment or disease treatment. Refer to the tables of valganciclovir dosing with impaired renal function and CMV prophylaxis and treatment protocols for renal, liver and lung recipients on the following pages. Valganciclovir is administered with food.

Ganciclovir IV Dose for ADULT Patients with Impaired Renal Function [(6)]

Creatinine Clearance (mL/min)	Ganciclovir IV Dosage (mg/kg) TREATMENT and PRE-EMPTIVE Dosage	Ganciclovir IV Dosage (mg/kg) PROPHYLAXIS Dosage
Greater and equal to 70	5 mg/kg/dose q 12h	5 mg/kg/dose q 24h
50 to 69	5 mg/kg/dose q 24h OR 2.5 mg/kg/dose q 12h	2.5 mg/kg/dose q 24h
25 to 49	2.5 mg/kg/dose q 24h	1.25 mg/kg/dose q 24h
10 to 24	1.25 mg/kg/dose q 24h	0.625 mg/kg/dose q 24h
Less than 10	1.25 mg/kg/dose 3 times weekly post dialysis	0.625 mg/kg/dose 3 times weekly post dialysis

Valganciclovir Oral TABLET Dose for ADULT and Adolescent Patients Greater Than 16 Years of Age with Impaired Renal Function [1]

Creatinine Clearance (mL/min)	Valganciclovir TABLETS PO TREATMENT and PRE-EMPTIVE Dosage	Valganciclovir TABLETS PO PROPHYLACTIC Dosage
Greater and equal to 60	900 mg PO twice a day	900 mg PO daily
40 to 59	450 mg PO twice a day	450 mg PO daily
25 to 39	450 mg PO daily	450 mg PO every 2 days
10 to 24	450 mg PO every 2 days	450 mg PO twice weekly

Valganciclovir Oral SOLUTION Dose for ADULT and Adolescent Patients Greater Than 16 Years of Age with Impaired Renal Function [1,16]

Creatinine Clearance (mL/min)	Valganciclovir SOLUTION PO TREATMENT and PRE-EMPTIVE Dosage	Valganciclovir SOLUTION PO PROPHYLACTIC Dosage
Greater and equal to 60	900 mg PO twice a day	900 mg PO daily
40 to 59	450 mg PO twice a day	450 mg PO daily
25 to 39	450 mg PO daily	225 mg PO daily
10 to 24	225 mg PO daily	125 mg PO daily
Less than 10	200 mg three times a week post dialysis	100 mg PO three times a week post dialysis

***** Valcyte (valganciclovir) oral solution is commercially available – use hazardous drug precautions *****

Valganciclovir Oral Dose for Pediatric Transplant Recipients Aged Four Months to 16 Years [7, 16]

Dose (mg) = 7 x BSA x CrCl, to a maximum dose of valganciclovir of 900mg once daily for CMV prophylaxis (Maximum: 900mg BID for CMV treatment)

$$\text{BSA } (m^2) = \frac{\sqrt{\text{height (cm) x weight (kg)}}}{3600}$$

CrCl estimate = GFR estimate = calculated as per new modified Schwartz equation

$$\text{New Modified Schwartz equation*} = \frac{0.413 \text{ x height (cm) x } 88.4}{\text{SCr mmol/L}}$$

*This equation can only be used under certain circumstances per BC Children's Hospital nephrologists.
*If calculated CrCl exceeds 120 mL/min/1.73 m^2, use a maximum of 120 mL/min/1.73 m^2 in dosage calculation.

CMV PROPHYLAXIS AND TREATMENT REGIMENS FOR KIDNEY AND KIDNEY-PANCREAS TRANSPLANT RECIPIENTS
(*SEE BELOW FOR PEDIATRIC NOTES*) (Nov 2018) [9-13 14]

DONOR	RECIP	PROPHYLAXIS	PRE-EMPTIVE TREATMENT asymptomatic	DISEASE TREATMENT symptomatic
Neg	Neg	No prophylaxis with **valganciclovir** If ATG is used for rejection, obtain CMV IgG prior to starting ATG. • CMV DNA viral load with routine bloodwork (maximum q weekly) for 12 months post-transplant and for an additional 6 months following any antiviral treatment.	CMV DNA viral load less than 35 IU/mL – no treatment CMV DNA viral load 35 to 1000 IU/mL; repeat CMV DNA viral load in 1 week CMV DNA viral load greater than 1000 IU/mL; start treatment: **valganciclovir 900 mg PO BID**. Dose adjust for renal function.^ • CMV DNA viral load and CBC with diff weekly while on treatment dose If CMV DNA viral load is increasing or patient becomes symptomatic, reduce immunosuppression and consider change to IV ganciclovir. Treat for at least 3 weeks and resolution of symptoms. End point of therapy is CMV DNA viral load less than 35 IU/mL for 2 consecutive readings (1 week apart). Following valganciclovir therapy: • CMV DNA viral load weekly for 2 months and then with routine BW for an additional 6 months even if it is beyond the first 12 months which is the minimum for testing. • Check for CMV IgG seroconversion after FIRST CMV episode. If the patient is CMV seropositive, follow the CMV Recipient Positive pathway guidelines for subsequent episodes	Any level of CMV DNA viral load; start treatment: **valganciclovir 900 mg PO bid or ganciclovir 5 mg/kg/dose IV q12h.** Dose adjust for renal function.^ • CMV DNA viral load and CBC with diff weekly while on treatment dose Treat for at least 3 weeks and resolution of symptoms. End point of therapy is CMV DNA viral load less than 35 IU/mL for 2 consecutive readings (1 week apart). Following valganciclovir therapy: • CMV DNA viral load weekly for 2 months and then with routine BW for an additional 6 months even if it is beyond the first 12 months which is the minimum for testing. • Check for CMV IgG seroconversion after FIRST CMV episode. If the patient is CMV seropositive, follow the CMV Recipient Positive pathway guidelines for subsequent episodes
Pos (Mismatch)	Neg	**Prophylaxis:** **valganciclovir 900 mg PO daily for 6 months.** Dose adjust for renal function^ **Lymphocyte Depleting Therapies for Acute Rejection:** **valganciclovir 900mg PO daily or ganciclovir 5 mg/kg/dose IV q24h for 3 months** Dose adjust for renal function.^ • CBC with diff q2wk (minimum) while on therapy. • CMV DNA viral load with routine bloodwork (maximum q weekly) for 12 months post-transplant and for an additional 6 months following any antiviral treatment.	CMV DNA viral load less than 35 IU/mL – no treatment CMV DNA viral load 35 to 1000 IU/mL; repeat CMV DNA viral load in 1 week CMV DNA viral load greater than 1000 IU/mL; start treatment: **valganciclovir 900 mg PO BID.** Dose adjust for renal function.^ • CMV DNA viral load and CBC with diff weekly while on treatment dose If CMV DNA viral load is increasing or patient becomes symptomatic, reduce immunosuppression and consider change to IV ganciclovir. Treat for at least 3 weeks and resolution of symptoms. End point of therapy is CMV DNA viral load less than 35 IU/mL for 2 consecutive readings (1 week apart). Following valganciclovir therapy: • CMV DNA viral load weekly for 2 months and then with routine BW for an additional 6 months even if it is beyond the first 12 months which is the minimum for testing. • Check for CMV IgG seroconversion after FIRST CMV episode. If the patient is CMV seropositive, follow the CMV Recipient Positive pathway guidelines for subsequent episodes	Any level of CMV DNA viral load; start treatment: **valganciclovir 900 mg PO bid or ganciclovir 5 mg/kg/dose IV q12h.** Dose adjust for renal function.^ • CMV DNA viral load and CBC with diff weekly while on treatment dose Treat for at least 3 weeks and resolution of symptoms. End point of therapy is CMV DNA viral load less than 35 IU/mL for 2 consecutive readings (1 week apart). Following valganciclovir therapy: • CMV DNA viral load weekly for 2 months and then with routine BW for an additional 6 months even if it is beyond the first 12 months which is the minimum for testing. • Check for CMV IgG seroconversion after FIRST CMV episode. If the patient is CMV seropositive, follow the CMV Recipient Positive pathway guidelines for subsequent episodes

DONOR	RECIP	PROPHYLAXIS	PRE-EMPTIVE TREATMENT asymptomatic	DISEASE TREATMENT symptomatic
Pos OR Neg	Pos	**Adults: No prophylactic valganciclovir** **Pediatrics: valganciclovir 900 mg po daily for 3 months.** Dose adjust for renal function.^ **During Lymphocyte Depleting Therapies:** **valganciclovir 900mg PO daily or ganciclovir 5mg/kg/dose IV q24h for 1 to 3 months.** Dose adjust for renal function.^ • CBC with diff q2wk (minimum) while on therapy. • CMV DNA viral load with routine bloodwork (maximum q weekly) for 12 months post-transplant and for an additional 6 months following any antiviral treatment.	CMV DNA viral load less than 35 IU/mL or 35-1000 IU/mL – no treatment. Repeat CMV DNA viral load as per protocol. CMV DNA viral load greater than 5000 IU/mL on a single reading or patient with rising viral loads on 2 consecutive measurements greater than 1000 IU/mL; start treatment: **valganciclovir 900 mg PO BID.** Dose adjust for renal function.^ • CMV DNA viral load and CBC with diff weekly while on treatment dose If CMV DNA viral load is increasing or patient becomes symptomatic, reduce immunosuppression and consider change to IV ganciclovir. Treat for at least 3 weeks and resolution of symptoms. End point of therapy is CMV DNA viral load less than 35 IU/mL for 2 consecutive readings (1 week apart). Following valganciclovir therapy: • CMV DNA viral load weekly for 2 months and then with routine BW for an additional 6 months even if it is beyond the first 12 months which is the minimum for testing.	**Any level of CMV DNA viral load; start treatment:** **valganciclovir 900 mg PO bid or ganciclovir 5 mg/kg/dose IV q12h.** Dose adjust for renal function.^ • CMV DNA viral load and CBC with diff weekly while on treatment dose Treat for at least 3 weeks and resolution of symptoms. End point of therapy is CMV DNA viral load less than 35 IU/mL for 2 consecutive readings (1 week apart). Following valganciclovir therapy: • CMV DNA viral load weekly for 2 months and then with routine BW for an additional 6 months even if it is beyond the first 12 months which is the minimum for testing.

^***Dose adjustment for valganciclovir/ganciclovir for patients with impaired renal function***. ***Click here***.

If leukopenia is thought to be due to valganciclovir and patient has been receiving prophylaxis for 4-6 months, stop valganciclovir and start weekly CMV DNA viral loads and CBC with diff. If patient is neutropenic (ANC<0.5) or has declining WBC counts on therapeutic valganciclovir, may need to start filgrastim 300mcg SC daily x 3 doses to increase the count and continue with valganciclovir for treatment. Do not dose reduce valganciclovir or ganciclovir for leukopenia. See BCT Filgrastim Neutropenia guideline here

CMV DNA Viral Load = number of International Units (IU) of CMV DNA virus per millilitre

Pediatric Patients:

- All samples should be tested at BC Children's lab since the CMV assay at Children's differs from the adult assay at St. Paul's lab
- BC Children's lab reports CMV viral load as copies/mL
- Pediatric goals of therapy is to treat until CMV viral load = 0 for two consecutive readings

CMV PROPHYLAXIS AND TREATMENT REGIMENS FOR LIVER TRANSPLANT RECIPIENTS
(SEE BELOW FOR PEDIATRIC NOTES) (Nov 2018) (9-13 14)

DONOR	RECIP	PROPHYLAXIS	PRE-EMPTIVE TREATMENT asymptomatic	DISEASE TREATMENT symptomatic
Neg	Neg	No prophylaxis with **valganciclovir** If ATG is used for rejection, obtain CMV IgG prior to starting ATG. • CMV DNA viral load weekly for 3 months post-transplant and for an additional 3 months following any antiviral treatment	CMV DNA viral load weekly: CMV DNA viral load less than 35 IU/mL – no treatment CMV DNA viral load 35 to 1000 IU/mL; repeat CMV DNA viral load in 1 week CMV DNA viral load greater than 1000 IU/mL; start treatment: **valganciclovir 900 mg PO BID**. Dose adjust for renal function.^ • CMV DNA viral load and CBC with diff weekly while on treatment dose If CMV DNA viral load is increasing or patient becomes symptomatic, reduce immunosuppression and consider change to IV ganciclovir. Treat for at least 3 weeks and resolution of symptoms. End point of therapy is CMV DNA viral load less than 35 IU/mL for 2 consecutive readings (1 week apart). **Secondary Prophylaxis:** may be considered for high risk patients* **valganciclovir 900 mg PO daily for 2 month.** Dose adjust for renal function.^ • CMV DNA viral load and CBC with diff q2wk (minimum) while on reduced therapy. Following valganciclovir therapy: • CMV DNA viral load weekly for 3 months • Check for CMV IgG seroconversion after FIRST CMV episode. If the patient is CMV seropositive, follow the CMV Recipient Positive pathway guidelines for subsequent episodes	Any level of CMV DNA viral load start treatment: **valganciclovir 900 mg PO bid or ganciclovir 5 mg/kg/dose IV q12h.** Dose adjust for renal function.^ • CMV DNA viral load and CBC with diff weekly while on treatment dose Treat for at least 3 weeks and resolution of symptoms. End point of therapy is CMV DNA viral load less than 35 IU/mL for 2 consecutive readings (1 week apart). **Secondary Prophylaxis:** may be considered for high risk patients* **valganciclovir 900 mg PO daily for 2 month.** Dose adjust for renal function.^ • CMV DNA viral load and CBC with diff q2wk (minimum) while on reduced therapy. Following valganciclovir therapy: • CMV DNA viral load weekly for 3 months • Check for CMV IgG seroconversion after FIRST CMV episode. If the patient is CMV seropositive, follow the CMV Recipient Positive pathway guidelines for subsequent episodes
Pos	Neg	**Adult Prophylaxis:** **valganciclovir 900 mg PO daily for 3 months.** Dose adjust for renal function^	Same as above	Same as above
(Mismatch)		**Lymphocyte Depleting Therapies for Acute Rejection:** **valganciclovir 900mg PO daily or ganciclovir 5 mg/kg/dose IV q24h for 3 months** Dose adjust for renal function.^ **Steroid Therapy for Acute Rejection:** valganciclovir 900 mg PO daily for 1 month. Dose adjust for renal function.^ • No CMV DNA viral load testing required during prophylaxis • CBC with diff weekly while on therapy Following valganciclovir therapy: • CMV DNA viral load weekly for 3 months post CMV prophylaxis and for additional 3 months following any antiviral treatment.		

DONOR	RECIP	PROPHYLAXIS	PRE-EMPTIVE TREATMENT asymptomatic	DISEASE TREATMENT symptomatic
Pos OR Neg	Pos	**Adults: No prophylaxis** **Lymphocyte Depleting Therapies for Acute Rejection:** **valganciclovir 900mg PO daily or ganciclovir 5mg/kg/dose IV q24h for 1 to 3 months.** Dose adjust for renal function.^ **Steroid Therapy for Acute Rejection:** **valganciclovir 900 mg PO daily for 1 month.** Dose adjust for renal function.^ • No CMV DNA viral load testing required during prophylaxis • CBC with diff weekly while on therapy Following valganciclovir therapy: • CMV DNA viral load weekly for 3 months post CMV prophylaxis and for additional 3 months following any antiviral treatment.	CMV DNA viral load less than 35 IU/mL or 35-1000 IU/mL – no treatment. Repeat CMV DNA viral load as per protocol. CMV DNA viral load greater than 5000 IU/mL on a single reading or patient with rising viral load on 2 consecutive measurements greater than 1000 IU/mL; start treatment: **valganciclovir 900 mg PO BID.** Dose adjust for renal function.^ • CMV DNA viral load and CBC with diff weekly while on therapy. If CMV DNA viral load is increasing or patient becomes symptomatic, reduce immunosuppression and consider change to IV ganciclovir. Treat for at least 3 weeks and resolution of symptoms. End point of therapy is CMV DNA viral load less than 35 IU/mL for 2 consecutive readings (1 week apart). Following valganciclovir therapy: • CMV DNA viral load weekly for 3 months	Same as above

^***Dose adjustment for valganciclovir/ganciclovir for patients with impaired renal function.*** ***Click here***

If leukopenia is thought to be due to valganciclovir and patient has been receiving prophylaxis for 4-6 months, stop valganciclovir and start weekly CMV DNA viral loads and CBC with diff. If patient is neutropenic (ANC<0.5) or has declining WBC counts on therapeutic valganciclovir, may need to start filgrastim 300mcg SC daily x 3 doses to increase the count and continue with valganciclovir for treatment. Do not dose reduce valganciclovir or ganciclovir for leukopenia. See BCT Filgrastim Neutropenia guideline here

CMV DNA Viral Load = number of International Units (IU) of CMV DNA virus per millilitre

***Secondary prophylaxis**

Defined as prolonged therapy with standard prophylaxis doses (e.g., once daily) after a successful treatment course. Use and duration should reflect the likelihood of recurrent CMV infection.

High risk patients:

- Serious tissue-invasive disease without viremia
- Multi-organ disease
- Gastrointestinal tissue-invasive disease
- Primary CMV infection
- High initial viral load
- Slow reduction in viral load on treatment
- Recurrent CMV disease
- Treatment of rejection during treatment for CMV disease
- High net state of immunosuppression

Pediatric Patients:

- All samples should be tested at BC Children's lab since the CMV assay at Children's differs from the adult assay at St. Paul's lab
- BC Children's lab reports CMV viral load as copies/mL
- Pediatric goals of therapy is to treat until CMV viral load = 0 for two consecutive readings

CMV PROPHYLAXIS AND TREATMENT REGIMENS FOR LUNG TRANSPLANT RECIPIENTS
(SEE BELOW FOR PEDIATRIC NOTES) (Nov 2018) [9-13 14]

DONOR	RECIP	PROPHYLAXIS	PRE-EMPTIVE TREATMENT asymptomatic	DISEASE TREATMENT symptomatic
Neg	Neg	• No prophylaxis with **valganciclovir** • CMV negative blood products • CMV DNA viral loads testing as indicated	CMV DNA viral load greater than 1000 IU/mL and the patient is **asymptomatic;** consider repeating viral load in 1 week depending on clinical situation **OR** start disease treatment protocol	Any level of CMV DNA viral load; start treatment: **valganciclovir 900 mg PO bid or ganciclovir 5 mg/kg/dose IV q12h.** Dose adjust for renal function.^ • CMV DNA viral load and CBC with diff weekly while on treatment dose Treat for at least 3 weeks and resolution of symptoms. End point of therapy is CMV DNA viral load less than 35 IU/mL for 2 consecutive readings (1 week apart). Following valganciclovir therapy: • CMV DNA viral load weekly for 12 weeks • Check for CMV IgG seroconversion after FIRST CMV episode. If the patient is CMV seropositive, follow the CMV Recipient Positive pathway guidelines for subsequent episodes
Pos (Mismatch)	Neg	**CMV Hyperimmune Globulin** 100 mg/kg day 0, then 100 mg/kg q3days for 3 weeks, then 50 mg/kg weekly for 8 weeks **Prophylaxis:** **valganciclovir 900 mg PO daily or or ganciclovir 5 mg/kg/dose IV q24h for 1 year.** Dose adjust for renal function^ • CMV DNA viral load and CBC with diff weekly while in hospital, then monthly post-transplant. When prophylaxis finished, intensify to weekly for 12 weeks and then resume monthly until 24 months. Then monitor every 3 months. **Lymphocyte Depleting Therapies for Acute Rejection:** **valganciclovir 900 mg PO daily or ganciclovir 5 mg/kg/dose IV q24h for 6 weeks.** Dose adjust for renal function.^ • CMV DNA viral load weekly for additional 2 months after prophylaxis finishes. **Steroid Therapy for Acute Rejection:** **valganciclovir 900 mg PO daily for 4 weeks.** Dose adjust for renal function.^ • CMV DNA viral load weekly for additional 2 months after prophylaxis finishes.	**CMV DNA viral load weekly, weeks 2 to 16:** For patients that have CMV symptoms regardless of viral load, start treatment CMV DNA viral load greater than 5000 IU/mL; then follow treatment protocol CMV DNA viral load between 35 to 5000 IU/mL and patient is **asymptomatic**, then consider repeating viral load in 1 week to see if it's a transient elevation **OR** start treatment: **valganciclovir 900 mg PO BID.** Dose adjust for renal function.^ • CMV DNA viral load and CBC with diff weekly while on treatment dose Treat for at least 3 weeks and resolution of symptoms. End point of therapy is CMV DNA viral load less than 35 IU/mL for 2 consecutive readings (1 week apart). (even if 16 weeks post-transplant) If relapse occurs, treat with **valganciclovir 900 mg PO BID for 12 weeks.** Following valganciclovir therapy: • CMV DNA viral load weekly for 8 weeks (even if 16 weeks post-transplant) • Check for CMV IgG seroconversion after FIRST CMV episode. If the patient is CMV seropositive, follow the CMV Recipient Positive pathway guidelines for subsequent episodes	Any level of CMV DNA viral load; start treatment: **valganciclovir 900 mg PO bid or ganciclovir 5 mg/kg/dose IV q12h.** Dose adjust for renal function.^ • CMV DNA viral load and CBC with diff weekly while on treatment dose Treat for at least 3 weeks and resolution of symptoms. End point of therapy is CMV DNA viral load less than 35 IU/mL for 2 consecutive readings (1 week apart). Following valganciclovir therapy: • CMV DNA viral load weekly for 12 weeks • Check for CMV IgG seroconversion after FIRST CMV episode. If the patient is CMV seropositive, follow the CMV Recipient Positive pathway guidelines for subsequent episodes

DONOR	RECIP	PROPHYLAXIS	PRE-EMPTIVE TREATMENT asymptomatic	DISEASE TREATMENT symptomatic
Pos OR Neg	Pos	**Prophylaxis:** **valganciclovir 900 mg PO daily or ganciclovir 5 mg/kg/dose IV q24h for 6 months.** • CMV DNA viral load and CBC with diff weekly while in hospital, then monthly post-transplant. When prophylaxis finished, intensify to weekly for 12 weeks and then resume monthly until 24 months. Then monitor every 3 months. **Lymphocyte Depleting Therapies for Acute Rejection:** **valganciclovir 900mg PO daily or ganciclovir 5mg/kg/dose IV q24h for 6 weeks.** Dose adjust for renal function.^ • CMV DNA viral load weekly for 2 months after prophylaxis finishes **Steroid Therapy for Acute Rejection:** **valganciclovir 900 mg daily for 4 weeks** • CMV DNA viral load weekly for 2 months after prophylaxis finishes	**CMV DNA viral load weekly, weeks 2 to 16:** For patients that have CMV symptoms regardless of viral load, start treatment CMV DNA viral load greater than 5000 IU/mL; then follow treatment protocol CMV DNA viral load between 35 to 5000 IU/mL and patient is **asymptomatic**, then consider repeating viral load in 1 week to see if it's a transient elevation **OR** start treatment: **valganciclovir 900 mg PO BID.** Dose adjust for renal function.^ • CMV DNA viral load and CBC with diff weekly while on treatment dose Treat for at least 3 weeks and resolution of symptoms. End point of therapy is CMV DNA viral load less than 35 IU/mL for 2 consecutive readings (1 week apart). If relapse occurs, treat with **valganciclovir 900 mg PO BID for 12 weeks.** Dose adjust for renal function.^ Following valganciclovir therapy: • CMV DNA viral load weekly for 8 weeks (even if past 16 weeks post-transplant)	**Any level of CMV DNA viral load; start treatment:** **valganciclovir 900 mg PO bid or ganciclovir 5 mg/kg/dose IV q12h.** Dose adjust for renal function.^ • CMV DNA viral load and CBC with diff weekly while on treatment dose Treat for at least 3 weeks and resolution of symptoms. End point of therapy is CMV DNA viral load less than 35 IU/mL for 2 consecutive readings (1 week apart). Following valganciclovir therapy: • CMV DNA viral load weekly for 12 weeks

^Dose adjustment for valganciclovir/ganciclovir for patients with impaired renal function. ***Click here***

If leukopenia is thought to be due to valganciclovir and patient has been receiving prophylaxis for 4-6 months, stop valganciclovir and start weekly CMV DNA viral loads and CBC with diff. If patient is neutropenic (ANC<0.5) or has declining WBC counts on therapeutic valganciclovir, may need to start filgrastim 300mcg SC daily x 3 doses to increase the count and continue with valganciclovir for treatment. Do not dose reduce valganciclovir or ganciclovir for leukopenia. See BCT Filgrastim Neutropenia guideline here

CMV DNA Viral Load = number of International Units (IU) of CMV DNA virus per millilitre

Pediatric Patients:

- All samples should be tested at BC Children's lab since the CMV assay at Children's differs from the adult assay at St. Paul's lab
- BC Children's lab reports CMV viral load as copies/mL
- Pediatric goals of therapy is to treat until CMV viral load = 0 for two consecutive readings

CMV PROPHYLAXIS AND TREATMENT REGIMENS FOR HEART TRANSPLANT RECIPIENTS (SEE BELOW FOR PEDIATRIC NOTES) (Jan 2019) [9-13 14]				
DONOR	**RECIP**	**PROPHYLAXIS**	**PRE-EMPTIVE TREATMENT Asymptomatic**	**DISEASE TREATMENT Symptomatic**
Neg	Neg	No prophylaxis with **valganciclovir** CMV DNA viral load with biopsy as per protocol schedule	CMV DNA viral load less than 35 IU/mL and the patient is **asymptomatic** – no treatment CMV DNA viral load 35 to 1000 IU/mL and patient is **asymptomatic**; then repeat CMV DNA viral load in 1 week. If rising consider treatment CMV DNA viral load greater than 1000 IU/mL start treatment For patients that have CMV symptoms regardless of viral load, start treatment	Any level of CMV DNA viral load start treatment: **valganciclovir 900 mg PO bid or ganciclovir 5 mg/kg/dose IV q12h.** Dose adjust for renal function.^ (use ganciclovir for moderate-severe disease or not tolerating PO) • CMV DNA viral load and CBC with diff weekly while on therapy. Treat for at least 3 weeks and resolution of symptoms. End point of therapy is CMV DNA viral load less than 35 IU/mL for 2 consecutive readings (1 week apart). Following valganciclovir therapy: • CMV DNA viral load weekly for 2 months, then with routine biopsies. • Check for CMV IgG seroconversion after FIRST CMV episode. If the patient is CMV seropositive, follow the CMV Recipient Positive pathway guidelines for subsequent episodes
Pos	Neg	**Prophylaxis:** **valganciclovir 900 mg PO daily for 3 months.** Dose adjust for renal function^ If not tolerating PO, then ganciclovir 5 mg/kg/dose IV Q24h until patient able to tolerate PO. Dose adjust for renal function.^ **ATG therapy for Acute Rejection:** **valganciclovir 900mg PO daily or ganciclovir 5 mg/kg/dose IV q24h for 3 months** Dose adjust for renal function.^ **Steroid therapy for acute rejection:** **valganciclovir 900 mg PO daily for 4 weeks.** • CBC with diff q2wk (minimum) while on therapy. After prophylaxis is complete: • CMV DNA viral load weekly for 2 months	CMV DNA viral load less than 35 IU/mL and patient is **asymptomatic** – no treatment CMV DNA viral load 35 to 5000 IU/mL and patient is **asymptomatic**; then repeat CMV DNA viral load in 1 week. If rising consider treatment CMV DNA viral load greater than 5000 IU/mL; start treatment For patients that have CMV symptoms regardless of viral load, start treatment	Any level of CMV DNA viral load start treatment: **valganciclovir 900 mg PO bid or ganciclovir 5 mg/kg/dose IV q12h.** Dose adjust for renal function.^ (use ganciclovir for moderate-severe disease or not tolerating PO) • CMV DNA testing and CBC with diff q weekly while on treatment dose Treat for at least 3 weeks and resolution of symptoms. End point of therapy is CMV DNA viral load less than 35 IU/mL for 2 consecutive readings (1 week apart). Following valganciclovir therapy: • CMV DNA viral load weekly for 2 months; then with routine biopsies • Check for CMV IgG seroconversion after FIRST CMV episode. If the patient is CMV seropositive, follow the CMV Recipient Positive pathway guidelines for subsequent episodes
(Mismatch)				

DONOR	RECIP	PROPHYLAXIS	PRE-EMPTIVE TREATMENT asymptomatic	DISEASE TREATMENT symptomatic
Pos OR Neg	Pos	**Adults: No prophylactic valganciclovir** **ATG therapy for Acute Rejection:** **valganciclovir 900mg PO daily or ganciclovir 5 mg/kg/dose IV q24h for 3 months** Dose adjust for renal function.^ **Steroid therapy for acute rejection:** **valganciclovir 900 mg PO daily for 4 weeks.** • CBC with diff q2wk (minimum) while on therapy. After prophylaxis is complete: CMV DNA viral load weekly for 2 months	CMV DNA viral load less than 35 IU/mL and patient is **asymptomatic** – no treatment CMV DNA viral load 35 to 5000 IU/mL and patient is **asymptomatic** – repeat CMV DNA viral load in 1 week. If rising, consider treatment CMV DNA viral load greater than 5000 IU/mL start treatment For patients that have CMV symptoms regardless of viral load, start treatment	**Any level of CMV DNA viral load** **valganciclovir 900 mg PO bid or ganciclovir 5 mg/kg/dose IV q12h.** Dose adjust for renal function.^ (use ganciclovir for moderate-severe disease or not tolerating PO) • CMV DNA testing and CBC with diff q weekly while on treatment dose. Treat for at least 3 weeks and resolution of symptoms. End point of therapy is CMV DNA viral load less than 35 IU/mL for 2 consecutive readings (1 week apart). Following valganciclovir therapy: • CMV DNA viral load weekly for 2 months until documented decreased viral load, then with routine biopsies.

^***Dose adjustment for valganciclovir/ganciclovir for patients with impaired renal function.*** ***Click here.***

If leukopenia is thought to be due to valganciclovir and patient is on prophylaxis for 4-6 months, stop valganciclovir and start weekly CMV DNA viral loads and CBC with diff. If patient is neutropenic (ANC<0.5) or has declining WBC counts on therapeutic valganciclovir, may need to start filgrastim 300mcg SC daily x 3 doses to increase the count and continue with valganciclovir for treatment. Do not dose reduce valganciclovir or ganciclovir for leukopenia. See BCT Filgrastim Neutropenia guideline here

CMV DNA VIRAL LOAD = number of International Units (IU) of CMV DNA virus per millilitre

Cardiac biopsies:

- Generally scheduled in the first 3 months post- transplant for Week 2,3,4,6,8,10 and 12.

Pediatric Patients:

- All samples should be tested at BC Children's lab since the CMV assay at Children's differs from the adult assay at St. Paul's lab
- BC Children's lab reports CMV viral load as copies/mL
- Pediatric goals of therapy is to treat until CMV viral load = 0 for two consecutive readings

AVAILABILITY

Valganciclovir hydrochloride is available as a 450 mg tablets and as a powder for oral solution, 50 mg/mL when reconstituted. Reconstituted solution is stable for 49 days when stored under refrigeration.

Valganciclovir is a potential teratogen and carcinogen; care must be taken to avoid contact with the skin or eyes. If contact occurs, skin should be washed thoroughly with soap and water [(1)].

REFERENCES

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Management Guidelines:

List of Management Guidelines	
Guideline 1	BK Virus
Guideline 2	Dental Procedure Prophylaxis
Guideline 3	Herpes Simplex Virus Prophylaxis
Guideline 4	Immunizations
Guideline 5	Pneumocystis jiroveci Prophylaxis (PJP)
Guideline 6	Post-transplant diarrhea
Guideline 7	Post-transplant neutropenia (see filgrastim section)

BK Virus:

BK virus has up to a 60-80% seroprevalence rate in adults due to a primary oral or respiratory exposure in childhood. In the immumocompromised renal transplant patient, BKV reactivation in the donor kidney could lead to viruria, viremia and nephropathy which could lead to graft failure.

Given the limited published studies on the management of BK virus, the following guideline outlines the current management considerations for BK viremia in British Columbia. However, individualized management made by the most responsible clinician(s) understanding the patient's immune and infectious risk is paramount.

General Principles:

- For patients with their first BK viral load in the detectable range, repeat viral load **1 week later** to verify result and establish that it is not rising rapidly. Once the patient has established BK viremia, monitoring more frequently than every second week (q2 weeks) is unlikely to change management.
- The therapeutic goal is to start the management protocol early to prevent the progression to BK nephropathy.
- The patient's primary transplant centre must be consulted for patients with complicated BK viral course (ie. those who do not rapidly clear BKV with reduction of immunosuppression and in whom further therapy is necessary or patients with a rise in serum creatinine).
- If increasing viral load and/or creatinine, perform renal biopsy (if not done already) and consult the patient's primary transplant center.
- IVIG infusion may be warranted for patients with concurrent rejection. This is a challenging management problem and should be co-managed with the primary transplant center
- The management considerations for pediatric patients may differ compared to adults, given their developing immune system, serologic status and pharmacodynamics to immunosuppressant therapy. These patients will be managed by the BC Children's Hospital Multi-Organ Transplant Program.
- For pediatric kidney recipients: Serologic testing for titre of BKV antibody in the recipient at the time of transplantation is suggested for stratification of infection risk and to guide treatment of incident BK viremia.

Monitoring and Management:

- Screen BK viral load q2 weekly for 16 weeks, then monthly until end of year two. (Except in patients who have ongoing viremia or have had viremia after the first year.)

- For screening of patients beyond year two

    - Continue screening monthly for 12 months from the last detectable BK viral load

- Screen all cases of unexplained acute rise in serum creatinine and at the time of renal biopsy.

- If viral load is **less than 1000 copies/mL:**
    - Continue screening at q2 weekly intervals. If this becomes a stable long term finding, monitor BK viral loads monthly.

- If viral load is **between 1000 and 5000 copies/mL:**
    - If viral load is within this range but rising (e.g. 1200 and one week later rises to 3500), reduce mycophenolate mofetil (MMF) or mycophenolate sodium dose by 50%.
    - Continue CNI (calcineurin inhibitor (cyclosporine/tacrolimus)).
    - Monitor BK viral load q2 weeks or monthly if stable.

- If viral load is **greater than 5000 copies/mL:**
    - Reduce MMF dose by 50%. If patient on steroid and rapidly rising viral load, consider stopping MMF. Repeat BK viral load q2 weeks.

    - If viral load continues to increase and patient is still on MMF:
        - **Routine Patient Scenario**: Stop MMF and continue CNI. Repeat BK viral load q2 weeks.
        - **High Risk Patient Scenario**: Stop MMF and continue CNI and **ADD** leflunomide for patients at high risk of rejection (e.g. transplant within 3 months, history of rejection or documented biopsy proven BKVN)
        - Repeat BK viral load q2 weeks.
    - If viral load continues to increase and patient is not on MMF, reduce CNI by 25-50%:
        - Target cyclosporine trough levels of 50-100 ng/mL or tacrolimus trough level of 3-4 ng/mL[1].
        - Add leflunomide, if not added already.
        - Repeat BK viral load q2 weeks.
    - If viral load continues to rise despite stopping MMF, reducing the CNI and adding leflunomide:
        - Stop CNI and **ADD** sirolimus.
        - Repeat BK viral load q2 weeks.

- If biopsy **proven BK virus nephropathy** (BKVN)
    - OPTION 1: Stop MMF, continue on CNI, **ADD** leflunomide
    - OPTION 2: Stop MMF and CNI, **ADD** sirolimus and leflunomide
    - Monitor viral load q2 weeks until stable viral load or undetectable.

- If increasing viral load and/or creatinine, perform renal biopsy (if not done already) and consult the patient's primary transplant center.

Therapeutic End Points:

- When viral load is **undetectable** for 2 readings:
    - If patient only reduced or stopped MMF, start adding or increasing MMF. Dose adjustments are made by 250 mg BID increments for MMF or 180 mg increments for mycophenolate sodium. Patients are rarely returned to full dose MMF. Often patients are maintained at 50-75% of their original dose. Continue to monitor q2 weeks for two months then monthly for one year.

    - If viral load remains less than 1000 copies/mL, continue to re-introduce MMF.

- If viral load is over 1000 copies/mL, reduce or discontinue MMF and monitor q 2 weekly, following above protocol.
- If the patient had any other changes to their immunosuppression regimen (e.g. reduction in CNI, addition of leflunomide or sirolimus), consult their **primary transplant centre** on how to re-introduce standard immunosuppression.
- In addition to ensuring adequate immunosuppression, consider discontinuing leflunomide once the BK viremia has resolved and the patient is stable.
- Ongoing BK management for patients with long term low levels of viremia should be co-managed with the primary transplant centre.

BK Viral Loads:

BK Viral Loads are run at St. Paul's Hospital in the virology lab from Monday to Friday. To get the fastest turnaround time for your centre, determine which day(s) your local laboratory ships specimens to St. Paul's Hospital. Blood will have to be drawn the day before as it needs to be frozen for shipping.

Leflunomide: There is only limited evidence for efficacy in BK viremia and BK nephropathy but the local experience has been favourable. As leflunomide has some immunosuppressant effects, treatment is often considered in conjunction with reduction in doses or changes to immunosuppression regimen.

Loading dose: 100 mg PO daily for 3 days. Patients should only be loaded when the BK viral load is rapidly rising or has established BK nephropathy. Otherwise, starting with the maintenance dose is appropriate for most patients.

Maintenance dose: 20 mg PO daily and titrate based on efficacy (BK VL reduction) and ADRs. Usual dose 20 to 60 mg PO daily. Sometimes every other day dosing is required due to side effects.

Drug Levels:

- **Routine drug level monitoring is <u>not</u> recommended based on current available evidence**. However, therapeutic drug monitoring may be of benefit in difficult situations when patients demonstrate a lack of therapeutic response or exhibit signs of drug toxicity.

  - A clear relationship between drug concentration and efficacy or toxicity is lacking for leflunomide, and its therapeutic range is not well established in the literature. In addition, steady state concentrations are achieved after 14-20 weeks of therapy[2] due to the drug's very long half-life. In contrast, efficacy and toxicity endpoints, such as renal function and BKV clearance, can be readily assessed in a timely manner.
  - Based on limited data, a therapeutic range for leflunomide's active metabolite (teriflunomide/A77 1726) is suggested to be trough levels of 40-100 mcg/mL
  - A mean trough level of 81.1 ± 14mcg/mL has been associated with a higher incidence of hemolysis. If drug level is indicated, suggest to check an initial level at least 2 weeks after starting therapy and then 1 month later to assess for stability and trend.

- If drug level for leflunomide is indicated (active metabolite A771 1726), send trough (pre-dose) sample to:

  Calgary Laboratory Services, #9, 3535 Research Rd. NW, Calgary AB, T2L 2K8, Phone: 403-770-3600
  (See sample requisition below)

Toxicity monitoring:

- CBC and differential, creatinine, AST, and ALT q4 weeks;
- Rash, diarrhea/GI upset

Contraindication:

- Pregnancy is contraindicated while taking leflunomide. Due to the extended half-life of the active metabolite, it may take several weeks/months to be eliminated. Contact the transplant clinic for more information.

References:

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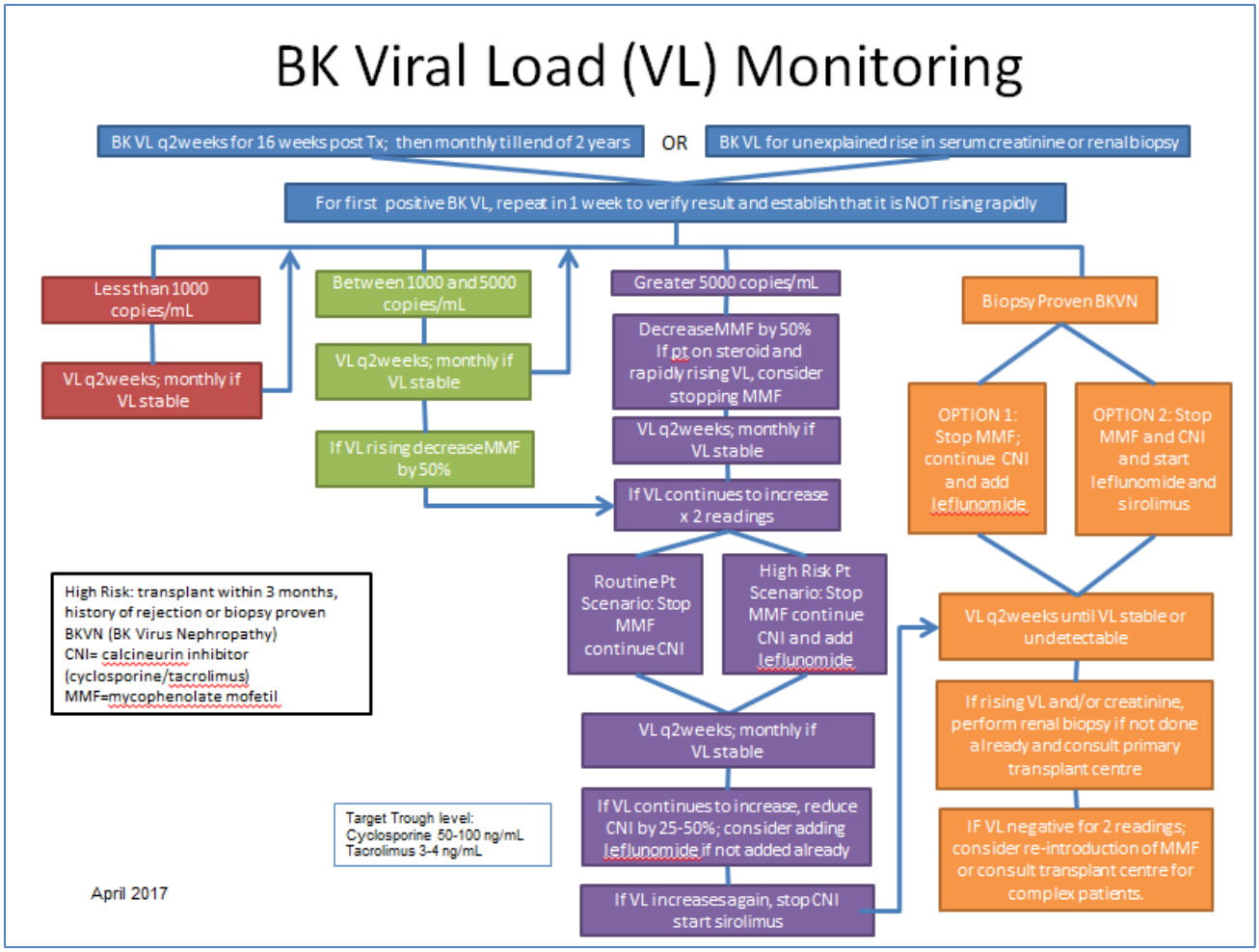

BK Viral Load (VL) Monitoring
BK VL q2weeks for 16 weeks post Tx; then monthly till end of 2 years
OR
BK VL for unexplained rise in serum creatinine or renal biopsy
For first positive BK VL, repeat in 1 week to verify result and establish that it is NOT rising rapidly
Less than 1000 copies/mL
VL q2weeks; monthly if VL stable
Between 1000 and 5000 copies/mL
VL q2weeks; monthly if VL stable
If VL rising decrease MMF by 50%
Greater 5000 copies/mL
Decrease MMF by 50% If pt on steroid and rapidly rising VL, consider stopping MMF
VL q2weeks; monthly if VL stable
If VL continues to increase x 2 readings
Routine Pt Scenario: Stop MMF continue CNI
High Risk Pt Scenario: Stop MMF continue CNI and add leflunomide
VL q2weeks; monthly if VL stable
If VL continues to increase, reduce CNI by 25-50%; consider adding leflunomide if not added already
If VL increases again, stop CNI start sirolimus
Biopsy Proven BKVN
OPTION 1: Stop MMF; continue CNI and add leflunomide
OPTION 2: Stop MMF and CNI and start leflunomide and sirolimus
VL q2weeks until VL stable or undetectable
If rising VL and/or creatinine, perform renal biopsy if not done already and consult primary transplant centre
IF VL negative for 2 readings; consider re-introduction of MMF or consult transplant centre for complex patients.
High Risk: transplant within 3 months, history of rejection or biopsy proven BKVN (BK Virus Nephropathy)
CNI= calcineurin inhibitor (cyclosporine/tacrolimus)
MMF=mycophenolate mofetil
Target Trough level:
Cyclosporine 50-100 ng/mL
Tacrolimus 3-4 ng/mL
April 2017

Hospital Name: _____
Dept. of Pathology and Laboratory Medicine
Address: _____
_____
Phone: _____
Fax:_____

Leflunomide Level Instructions

Collection Date _____

Time_____

Collected by_____

Container: **RED TOP 1-3.5mL**
Test Code: **DISPO** – Leflunomide level

Special Instructions for Laboratory Staff

- allow blood to clot for approx 30min
- centrifuge at 1200g for 10min
- transfer serum to 12 x 75 aliquot tube (minimum volume required is 1 mL)
- freeze at **-20°C or colder**

Accessioned by:_____

Ship frozen sample on Dry Ice to:

Accession – DSC
Calgary Laboratory Services
#9, 3535 Research Rd. NW
Calgary AB, T2L 2K8
Phone: 403-770-3600

SEND THIS REQUISITION WITH THE SAMPLE

For Calgary Lab:
Please forward results to the phone/fax listed above: Attn:
_____

Dental Procedure Prophylactic Antibiotics

The American Heart Association Guidelines for the Prevention of Infective Endocarditis: Recommend antibiotic prophylaxis before dental procedures ONLY for patients who have a history of previous infective endocarditis, or who have had cardiac valve replacement, or surgically constructed pulmonary shunts, or conduits. *(*Journal of the American Heart Association, Circulation 2007*; 116:1736-1754)* American Dental Association – Antibiotics Prophylaxis Prior to Dental Procedures

Prophylactic antibiotic coverage for dental procedures is recommended ONLY for the following transplant recipients:

- Prosthetic cardiac valve, including transcatheter-implanted prostheses and homografts
- Prosthetic material used for cardiac valve repair, such as annuloplasty rings and chords
- Previous history of infective endocarditis
- Congenital heart disease (CHD)
  - Unrepaired cyanotic CHD
  - 6 months following repair of CHD with any prosthetic material or device
  - Repaired CHD with residual defects
- Cardiac transplant recipients who develop cardiac valvulopathy

Recommended Antibiotic Regimens for a Dental Procedure

Situation	Antibiotic	Regimen: Single dose 30 to 60 min prior procedure^	
		Adults	**Children**
Oral	Amoxicillin	2 grams	50 mg/kg
Unable to Take Oral Medication	Ampicillin OR Cefazolin or Ceftriaxone	2 grams IV or IM 1 gram IV or IM	50 mg/kg IV or IM 50 mg/kg IV or IM
True Allergy to Penicillin Allergic to Penicillin or Ampicillin – Oral	Cephalexin***#** OR Clindamycin OR Azithromycin or Clarithromycin	2 grams 600 mg 500 mg	50 mg/kg 20 mg/kg 15 mg/kg
Allergic to Penicillin or Ampicillin and Unable to Tak Oral Medication	Cefazolin or Ceftriaxzone**#** OR Clindamycin	1 gm IV or IM 600 mg IV or IM	50 mg/kg IM or IV 20 mg/kg IV or IM

***** Or other first or second generation oral cephalosporin in equivalent adult or pediatric dosage
# Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema or urticaria with penicillin or ampicillin
^ If the patient forgets to take the dose prior to the dental procedure, the dosage may be administered as soon as possible, up to 2 hours after the procedure.

Herpes Simplex Virus (HSV) Prophylaxis

The current incidence of HSV related infections is much lower than those reported in the pre-CMV prophylaxis era in the 1990s.[1] HSV infections may occur any time post-transplant given the ongoing need for immunosuppression. However, data from the 1980s in renal *transplant recipients suggested that the first month post-transplant was the high risk period* for severe disease. Prophylaxis has only been studied in this time frame.[2]

HSV serology and antibody titers are not routinely recommended. For this protocol, we are assuming all adult recipients are HSV sero-positive.

For CMV D-/R- patients induced with ATG and are not receiving valganciclovir prophylaxis for CMV, valacyclovir prophylaxis should be considered immediately post-transplant.

- Valacyclovir 500mg PO BID x 3 months.

Valacyclovir is a BC Pharmacare benefit drug and therefore is not covered on the BC Transplant Formulary.

References:

1. Netchiporouk E, Tchervenkov J, Paraskevas S, Sasseville D, Billick R. Evaluation of herpes simplex virus infection morbidity and mortality in pancreas and kidney-pancreas transplant recipients. Transplant Proc 2013;45,3343-7.

2. Wilck MB, Zuckerman RA and the AST Infectious Diseases Community of Practice. Herpes simplex virus in solid organ transplantation. Am J Transplant 2013;13:121-7.

Immunization

Refer to most current BCCDC recommended Immunization of Special Populations Program as per BCCDC Communicable Disease Control, Immunization Program, Section III - Immunization of Special Populations

General Principles for Immunization of the Immunocompromised Patients

Maximize benefit while minimizing harm.

- There is potential for serious illness and death in the under-immunization of immunocompromised people and every effort should be made to ensure adequate protection through immunization.

Make no assumptions about susceptibility or protection.

- A history of childhood infection or previous vaccination may be irrelevant.

Vaccinate at the time when maximum immune response can be anticipated.

- Vaccines may be less effective when administered during the period of altered immunocompetence. Individuals who are fully immunized may remain at risk for vaccine-preventable diseases.
- Vaccinate early when immunologic decline is predictable.
- Delay vaccination if the immunodeficiency is transient (if this can be done safely).
- Primary health care provider may decide to stop or reduce immunosuppressive therapy to permit better vaccine response (if this is appropriate).

Consider the vaccination environment broadly.

- Vaccinate family and care givers when individuals need protection (i.e., against influenza).

Avoid live vaccines unless:

- Data are available to support their used and
- The risk of natural infection is greater than the risk of vaccination.

Administer routine boosters as indicated.

- The degree and duration of vaccine-induced immunity are often reduced in immune compromised individuals.

Consider the used of passive immunizing agents.

These include:

- Immune globulin (Ig)
- Intravenous immune globulin (IVIg)
- The several “pathogen-specific” Ig preparation that are available (i.e., varicella zoster Ig, tetanus Ig).

Ideally a solid organ transplant recipient should receive all vaccines before transplantation occurs. However some patients may not have been fully vaccinated prior to transplantation.

There is a potential for serious illness and death in both the under immunization and over immunization of solid organ transplant recipients. Immunization of those with significant immunodeficiency should be performed only in consultation with experts. Following transplantation
previous immunizations should be assessed and vaccinations offered to complete the schedule. Immunization should begin or resume at least six to twelve months after transplantation. If not vaccinated prior to kidney transplant patients should be immunized for:

- Td or Tdap
- IPV
- Hepatitis B
- Meningococcal (conjugate)
- Pneumococcal (conjugate and/or polysaccharide)
- Hib
- Influenza

Booster doses:

- Td every 10 years for life
- Influenza every year for life
- Pneumococcal once only revaccination after five years
- Meningococcal Polysaccharide every three years for life

All live vaccines (such as MMR and Varicella) are contraindicated following transplantation except in certain circumstances.

Pneumocystis jiroveci Prophylaxis (PJP/PCP)

Adult Patients:

Patients are prescribed prophylactic trimethoprim-sulfamethoxazole (Cotrimoxazole, Septra) for Pneumocystis Pneumonia while receiving high dose immunosuppression.

- Cotrimoxazole single strength (Septra) 1 tablet PO daily or Cotrimoxazole double strength (Septra DS) 1 tablet PO on Mondays, Wednesdays and Fridays.
- Cotrimoxazole (or alternate PJP/PCP therapy) should be administered for at least one year post transplant. For patients tolerating cotrimoxazole, consider lifelong therapy.
- Re-introduce cotrimoxazole (or alternate PJP prophylaxis) anytime patients are receiving increased immunosuppression or undergoing therapy for rejection.
- If patients are allergic to cotrimoxazole, consult the primary transplant centre for alternative prophylaxis.
- Alternatives include:
    - Dapsone 100 mg PO three times a week.
- If patient is allergic to dapsone, alternative is:
    - pentamidine 300 mg inhalation administered through aerosolized nebulizer every 4 weeks for 1 year post transplant. Re-evaluate possible restarting of cotrimoxazole.

Pediatric Patients (consult BCCH Transplant Program for advice on PJP therapy)

Patients are prescribed prophylactic trimethoprim-sulfamethoxazole (Cotrimoxazole, Septra®) for Pneumocystis Pneumonia while receiving high dose immunosuppression.

Administer 5 mg/kg/day trimethoprim component ONCE daily or divided bid on 3 consecutive days per week OR on Monday, Wednesday and Friday. Maximum 2 tablets per day or 20 mL per day.

Cotrimoxazole should be administered for at least one year post transplant.

Re-introduce cotrimoxazole (or alternate PJP prophylaxis) anytime patients are receiving increased immunosuppression or undergoing therapy for rejection.

If patients are allergic to cotrimoxazole:

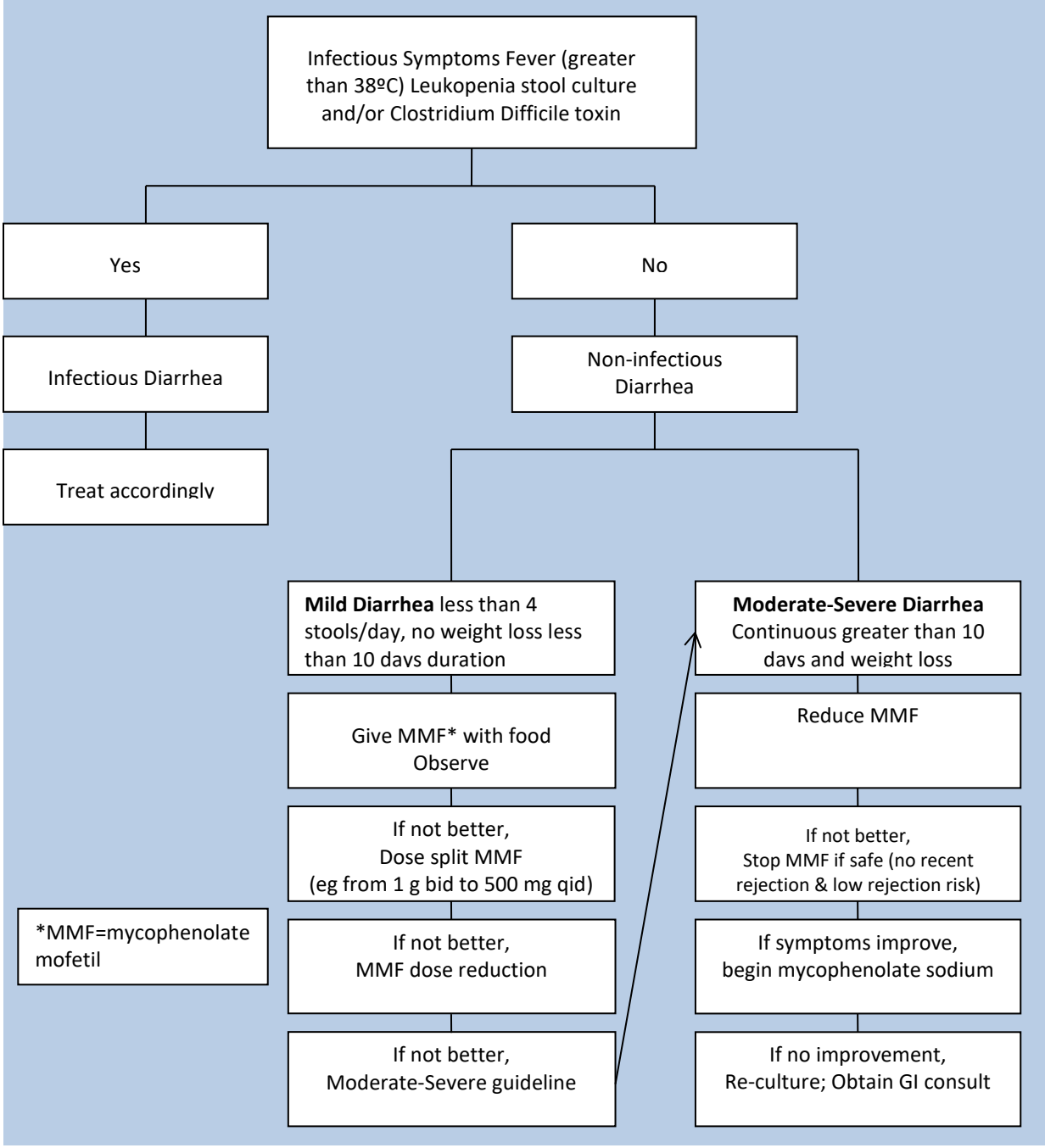
- dapsone 2 mg/kg/day PO three times a week. Maximum: 100 mg per dose.

If patient is allergic to dapsone:

- Pentamidine pediatric dose: age less than 5 years: 8 mg/kg/dose via nebulizer every 4 weeks. Maximum: 150 mg per dose.
- Age greater than 5 years: 300 mg via nebulizer every 4 weeks.

POST-TRANSPLANT DIARRHEA MANAGEMENT

Diarrhea is a frequent problem in post-transplant patients. One must make a distinction between medication induced and infectious diarrhea.



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Maes B et al. Severe diarrhea in renal transplant patients: results of the DIDACT study. *Am J Transplant.* 2006:6; 1466-1472.

Appendices

List of Appendices	
Appendix A	BCT Fax Form – Application for Sirolimus Renal Transplant Recipients
Appendix B	BCT Fax Form – Application for Sirolimus Heart Transplant Recipients
Appendix C	BCT Fax Form – Application for Erythrocyte Stimulating Agents
Appendix D	BCT Fax Form – Application for filgrastim (G-CSF)

Appendix A

Application for Sirolimus RENAL Transplant Recipients

Please complete and fax to BCT Pharmacist (604) 877-2111

DATE:

TO:

FROM:

BCT#: _____ Last Name: _____First Name: _____

Hospital: _____ Nephrologist_____

Indications for Sirolimus Use:

1. ☐ Patient was enrolled in a sirolimus clinical study.

2. ☐ Patient has developed calcineurin inhibitor toxicity:
   a) Biopsy-proven, severe nephrotoxicity, while on calcineurin inhibitors despite blood concentrations within therapeutic range. Increase in serum creatinine must be at least 50% above baseline.

   ☐ Cyclosporine
   ☐ Tacrolimus

   b) Neurotoxicity:

   ☐ Cyclosporine (date _____)
   ☐ Tacrolimus (date_____)

3. ☐ Patient has developed severe refractory BK virus-induced nephropathy while on a calcineurin inhibitor

4. ☐ Pediatric patient with refractory rejection.

5. ☐ Patient has recurrent skin cancer. ☐ Patient has renal cancer. ☐ Patient has another cancer:

   Specify other cancer type: _____

PRIOR TO BEGINNING SIROLIMUS FOR SKIN CANCER INDICATION PATIENT MUST BE DISCUSSED WITH THE PRIMARY TRANSPLANT CENTRE

For other cancers: Sirolimus MUST be approved by a transplant nephrologist at the primary transplant centre: Approved by _____ Date (_____) at VGH ☐ SPH ☐

Physician's Signature: _____ Date: _____

Approval by BCT: _____ Date: _____

REV: OCT 2014

Appendix B

Application for Sirolimus HEART Transplant Recipients

Please complete and fax to BCT Pharmacist (604) 877-2111

DATE:

TO:

FROM:

BCT #:_____

Name: Last: _____ First: _____

Hospital: _____ Cardiologist: _____

Indications for Sirolimus Use:

1. ☐ In addition to a calcineurin inhibitor in patients who have recurrent or persistent transplant rejection within the first year post transplant

2. ☐ Patient has developed cardiac allograft vasculopathy (CAV)

3. ☐ Patient has developed calcineurin inhibitor neurotoxicity or nephrotoxicity

5. ☐ Patient has developed cancer. Type:_____

6. ☐ Patient is following an out-of-province protocol.

Physician's Signature: _____ Date: _____

Approval by BCT: _____ Date: _____

REV: NOV 2014

Appendix C

British Columbia Transplant
West Tower, 3rd Floor,
555 West 12th Avenue,
Vancouver, B.C. V5Z 3X7

Telephone: (604) 877-2240
Fax: (604) 877-2111

APPLICATION FOR ERYTHROPOIETIN/Eprex® or DARBEPOETIN/Aranesp®

Please fax to BC Transplant at (604) 877-2111 Attn: BC Transplant Pharmacist

Erythropoietin and darbepoetin are indicated for use in kidney/kidney-pancreas transplant recipients who:

1. have a failing graft post transplant, or pre-transplant approved for transplant **and** are not on dialysis,
2. **and** have one symptom of anemia (fatigue, exercise intolerance, angina, impaired cognition).
3. **and** they must meet **ALL** the following lab criteria
   - i) glomerular filtration rate less than 50 mL/min by eGFR (based on MDRD equation)
   - ii) hemoglobin less than 95 g/L
   - iii) transferrin saturation (TSAT) 22% or greater

- All the lab criteria MUST be met before patient is initiated on Erythropoietin or Darbepoetin.
- For more information on the BC Transplant guidelines for ESAs: click here

BCT ID #: _____

Name: Last:_____ First: _____

Date of Birth: mo____ day____year_____ Sex: male _____ female _____

Hospital:_____ Nephrologist:_____

Patient is: ☐ **on transplant wait list** ☐ **post transplant has a failing graft**

Request for: ☐ **Erythropoietin (Eprex®)** ☐ **Darbepoetin (Aranesp®)**

Weight:	_____ kg
*Hemoglobin:	_____ g/L
Serum Creatinine:	_____ micromol/L
*Creatinine Clearance/eGFR:	_____ mL/min/1.73 m^2
*Transferrin Saturation (TSAT):	_____ %
Serum Ferritin:	_____ micromol/L

*required data

Physician's Signature: _____ Date: _____

Approval by BCT: _____ Date:_____

Rev:April 2017

A

Appendix D

Filgrastim (G-CSF, Grastofil) Data Collection-Prescription

1. Provider/Clinic to complete data collection sections and to forward prescription to BC Transplant Pharmacy

2. BC Transplant Pharmacy to dispense and fax form to BC Transplant office *Fax: 604-877-2111*

BCT ID:

Name:

PHN:

Organ group: ☐ Heart ☐ Kidney ☐ Liver ☐ Lung ☐ Pancreas/Islet Requesting clinic: _____

Assessment: please include dose adjustments if applicable

(dd-mmm-yy)	Date:	Date:	Date:	Date:	Date
WBC: (10^9/L)					
Neutrophil: (10^9/L)					
azathioprine					
cyclosporine					
cotrimoxazole (SS) 400/80					
mycophenolate (MMF / sodium)					
prednisone					
sirolimus					
tacrolimus (BID / OD)					
valganciclovir					
tacrolimus					

Indication(s) for filgrastim:

☐ Neutrophil < 0.5

☐ Febrile neutropenia

☐ Other:

_____

☐ If transplant medication adjustments cannot be made, please indicate reason:

_____

Prescription: ☐ 1st course – recommend 300 mcg dose for first course
☐ 2nd course

*If neutrophils not responding after 2nd course in a 12 month period, please consult BCT and hematology
*For pediatric patients at BC Children's – please supply Neupogen brand filgrastim

☐ filgrastim (Grastofil) 300 mcg SC daily X 3 days

☐ filgrastim (Grastofil) 480 mcg SC daily X 3days

Pharmacy: ☐ VGH ☐ SPH ☐ BCCH ☐ RJH ☐ Abb ☐ Nan ☐ Lang ☐ Kam ☐ Kel ☐ Pen ☐ PG ☐ Trl ☐ Sur

Prescriber signature Print Name College ID Date

Pharmacy: Please fax completed form to BC Transplant office: Fax: 604-877-2111 Attn: Pharmacy Coordinator