London Health Sciences Centre
Multi-Organ Transplant Program

PHYSICIAN GUIDELINES:
LONG-TERM CARE OF LIVER TRANSPLANT RECIPIENTS

These guidelines will help facilitate the care of liver transplant recipients. Topics include clinical issues, recurrent diseases, immunosuppressive medications, follow-up care, and contact with the transplant program.

Clinical Issues

Cellular Rejection: Cellular rejection, often referred to as acute rejection, occurs in approximately 15-25% of patients. Although rejection is most likely to develop within the first few months after transplantation, it can occur at any time.

Rejection can be associated with fever and malaise; however, often there are no clinical signs and it is noticed by routine blood work. A rise in AST, ALT and/or alkaline phosphatase may be noted. Many transplant patients have AST and ALT levels that are slightly abnormal over the long term. The pattern or trend is more important than an absolute level.

A rising level of enzymes is suggestive of rejection. When this is observed, the Prograf or cyclosporine level should be checked to ensure that it is at a therapeutic level and that the patient is compliant with taking medications. Along with potential noncompliance, other considerations include CMV disease, recurrence of primary disease, biliary stricture and drug toxicity. Also, patients with hepatitis C frequently have wide fluctuations in enzymes after transplant. Often a liver biopsy is warranted in this group to distinguish HCV from rejection, as management differs between the two.

A liver biopsy is the most definitive diagnostic aid, and it should be performed when in doubt. If confirmed, rejection is treated with tweaking of immunosuppression and the target dose range should be increased. Sometimes high-dose steroids tapering to the pre-treatment dosage over 10-14 days is required. The level of liver enzymes should improve within 5 days although it may not be in the normal range.

Steroid-Resistant Rejection: Steroid-resistant rejection rarely occurs, but when it does, consultation with the transplant team is warranted.

Ductopenic Rejection: Ductopenic rejection, often referred to as chronic rejection, occurs in <10% of patients, but it is the most common cause of re-transplantation. Biochemically, rising alkaline phosphatase is the most common feature with histopathology showing disappearance of bile ducts. Treatment options include manipulating immunosuppression and adding ursodeoxycholic acid (750-1000 mg/day).

Infection: Infection is common in the immune-suppressed patient. General good hygiene (hand washing) and avoiding individuals with obvious infectious symptoms is the mainstay of prevention. Work-up and treatment is very similar to non-transplant patients. CMV disease may occur after liver transplantation with the highest risk patients being CMV negative but receiving an organ from a CMV-positive donor. A strategy of pre-emptive therapy, such as oral valganciclovir, is often used in these patients. This treatment delays, but does not remove, the risk of CMV infection. Symptoms of CMV-related problems include fever, malaise, headache, leukopenia, myalgia, elevated liver enzymes, dyspnea, cough, diarrhea, or retinitis. The diagnosis can be made by CMV quantifiable PCR analysis in the blood, immunohistochemical staining of liver biopsy,

bronchial lavage or intestinal biopsies. Patients with significant CMV disease are usually given intravenous ganciclovir therapy. For resistant or recurrent infections, referral to an infectious diseases specialist may be helpful.

Renal Dysfunction: A known side effect of Prograf or cyclosporine therapy is potential kidney impairment. Both BUN and creatinine are poor markers of renal impairment. A radionucleotide GFR may provide more accurate assessment of kidney function. Often the treatment of choice is lowering the dose of the offending agent and assessing for other nephrotoxic agents, such as NSAIDs.

Hypertension: Many patients who take Prograf or cyclosporine develop hypertension. If the drug levels are maintained within a therapeutic range, hypertension can generally be controlled using this hypertension protocol. Optimal drug levels should not be compromised as rejection could result. For adult patients, the drug of first choice should be labetalol 100 mg PO BID. Compared to atenolol, labetalol is more effective with no need for dose adjustment in patients with renal impairment. A salt-restricted diet of 2 g per day should also be considered.

ACE Inhibitors: ACE inhibitors should be used with caution because of their effect on renal dysfunction and hyperkalemia.

Hyperkalemia: Persistent hyperkalemia is an occasional problem. With serum potassium levels repeatedly above 5.5, hyperkalemia should be treated by:

1) Reducing Prograf dosage, while maintaining appropriate therapeutic levels, and
2) Adding sodium polystyrene sulfonate (Kayexalate) 15-30 PO BID

Ascites: Patients who have ascites preoperatively may continue to accumulate ascites for several months after their transplant. A low-sodium diet (2 g) and diuretics, such as furosemide or spironolactone, are generally the preferred treatment. If ascites persist, the transplant team should be notified, and a Doppler ultrasound of the liver will likely be done.

Hypomagnesaemia: Hypomagnesaemia is a frequent complication. Magnesium supplementation may include dietary sources (such as peanuts or peanut butter) or medications; for example, magnesium gluconate 500 mg 2-4 times daily or magnesium-rich antacids may be ordered.

Aluminum-containing antacids or loperamide may be required to counteract the cathartic effect of these drugs. Please be mindful that mycophenolate can bind to aluminium and magnesium ions in the GI tract and form a less soluble complex, thereby reducing the amount of medication that is absorbed. It is best to space the administration of these medications if they are given orally; for example, mycophenolate is usually dosed at 08:00 and 20:00 so prescribe supplements at 12:00, 17:00 and/or 22:00.

Bile Duct Strictures: Bile duct strictures can occur early or late after transplant, and are usually identified by a rise in alkaline phosphatase. This can be accompanied by a rise in AST and ALT. Strictures can develop for various reasons including anastomotic narrowing, ischemic injury due to blood flow changes in the recipient, or preservation ischemia associated with the donor organ. If a stricture is suspected, surgical records should be checked to determine if the patient has duct-to-duct anastomosis or Roux-en-Y anastomosis (common with sclerosing cholangitis). With a duct-to-duct anastomosis, an endoscopic evaluation with ERCP should be performed. A percuataneous transphepatic cholangiogram may be necessary for patients with Roux-en-Y.

Post-Transplant Neoplastic Diseases: Post-transplant lymphoproliferative disorder (PTLD) occurs after liver transplantation in approximately 3% of patients. It can occur in many sites (tonsils, stomach, and mediastinum) but is commonly discovered as palpable lymphadenopathy. Suspicious nodes should be biopsied. Pathology can distinguish between polyclonal lesions, which can respond to reduction or removal of immunosuppression, and monoclonal lesions, which have a more aggressive course usually requiring chemotherapy. If lymphoma is proven, the patient should have a chest CT, abdominal CT scan, and bone marrow biopsy. A referral to an oncologist or haematologist may be necessary for chemotherapy assessment. Ideally, all immunosuppression is reduced and liver enzymes are closely monitored. Skin cancer is the most common cancer after transplant, and patients are encouraged to take precautions. Annual skin assessment should be done during regular health check-ups. Annual screening for transplant patients with a history of previous cancer (excluding HCC), IBD or PSC is recommended. All patients must be monitored for the development of colon, breast and prostate carcinomas as per screening protocols in the general population.

Obesity: Like the general population, obesity is a growing problem following transplantation. The resultant development of cardiac disease, diabetes, hyperlipidemia and steatohepatitis all bring their own set of health issues. Patients should be counselled on weight reduction and healthy lifestyle behaviours. We suggest a low carbohydrate diet.

Recurrent Diseases

Hepatitis B: Clinical recurrence can be substantially reduced with the use of nucleoside analogues (e.g. lamivudine 100 mg PO daily) in addition to HBIG. Viral suppression is important to prevent a flare or recurrence of disease.

Hepatitis C: Recurrence of hepatitis C is universal. Recurrent cirrhosis occurs in approximately 40% of patients within 5 years of transplant. Hepatitis C treatment is now >95% effective for all genotypes. Additionally, the ability to eradicate the virus before transplant will limit the recurrence rate following transplant. In <5% of patients, a rapid and devastating type of recurrence called fibrosing cholestatic hepatitis C may occur, usually within the first year after transplant. If you suspect this, you should notify the transplant team immediately.

Hepatocellular Carcinoma: Recurrence of HCC occurs in approximately 20% of patients. Recurrence is most likely in patients with tumours >5 cm, multi-nodular tumours, or when vascular invasion has been identified. Today, many adjuvant therapies are available to patients while they await transplantation, in an attempt to limit the above factors. Patients transplanted for HCC should have surveillance imaging every 6 months after transplant to monitor for recurrence.

Autoimmune Hepatitis: This disease is treated with immunosuppression; however, in a subset of the transplant population, recurrence happens. Optimization of immunosuppression is first-line therapy, and occasionally re-transplant is required.

Primary Biliary Cholangitis: This can occur in up to 20% of patients, yet is mild. Treatment with ursodiol is recommended. PBC recurrence rarely warrants re-transplantation.

Primary Sclerosing Cholangitis: PSC recurrence is approximately 20%, and it can lead to the need for re-transplantation in some patients. Biliary strictures have been reported following liver transplantation for sclerosing cholangitis and also for other liver diseases. Bile duct ischemia is another possible cause of this problem. Some patients will have recurrent cholangitis and are managed on long-term antibiotics.

Alcoholic Liver Disease: Recurrent alcohol use is likely under-reported but does occur in patients transplanted for alcoholic liver disease. Early diagnosis with referral for counselling and formal rehabilitation is recommended.

NASH: Because non-alcoholic steatohepatitis can recur after transplantation, it is important to emphasize a healthy lifestyle and weight management as a means of prevention. Astute management of lipids and diabetes is also important in preventing occurrence.

Immunosuppression

The standard immunosuppressive regimen for new liver transplant recipients is Prograf® (tacrolimus), CellCept® (mycophenolate), and prednisone. Some of our long-term patients continue to take cyclosporine.

It's important to remember that prescription and non-prescription medications can affect how well anti-rejection drugs work. Patients should not use herbal medications, and they should check with a pharmacist before taking over-the-counter medications, such as cold capsules, aspirin, cough syrups and vitamins. It is also strongly recommended that patients do not eat or drink products with grapefruit due to drug interactions. For potential drug interactions, see page 8 (Prograf) and page 9 (cyclosporine).

Tacrolimus (Prograf®):
Prograf is now used as the primary immunosuppressive drug for liver transplantation. Usually taken orally every 12 hours, Prograf is often combined with CellCept and prednisone to prevent rejection. It's important for patients to remember that not all community pharmacies stock Prograf. Patients should always have a 2-3 week supply of medications, and they should contact their community pharmacy for a refill as soon as their medication begins to run low.

After transplant, the Prograf level in blood is measured so that appropriate dosage changes can be made. The aim is to ensure enough drugs are given to prevent rejection, but not too much in order to minimize potential side effects. Side effects may include headache, tremors, elevated potassium in the blood, high blood pressure, and decreased kidney function. Prograf also makes some patients more sensitive to touch, causes numbness or tingling especially around the mouth, and can elevate blood sugar levels.

Prograf interacts with many other medications. Patients need to check with their doctor or pharmacist before taking any new prescribed or over-the-counter medications to ensure that their anti-rejection drugs will not be affected (see page 8). High levels can lead to renal toxicity and may increase the nephrotoxicity of other agents. Knowledge of drug interactions is incomplete and this possibility should be considered whenever there is an unexplained change in an otherwise stable series of Prograf levels.

(**Immunosuppression … continued)**

General guidelines for trough levels:

Months 0-3	7-10 ng/ml
>3 months	4-7 ng/ml
> 1 year	<5 ng/ml

Please note that individualized dosing is important, and is based on the underlying liver disease and co-morbidities. LHSC's Pharmacy provides more detailed information about Prograf.

Mycophenolate (CellCept®):
CellCept must be given with other anti-rejection drugs, for example, Prograf and prednisone. It is taken orally every 12 hours, either with or without food as long as it is done consistently.

Stomach upset and diarrhea are the most common side effects so taking with food may help patients tolerate the medication. Patients may also experience heartburn, acne, tremors, constipation, or headache. This drug may lower some blood cell counts, especially white blood cells. It's important that patients have their blood checked regularly and keep all clinic appointments.

Many transplant patients have had healthy babies while taking anti-rejection drugs; however, mycophenolate can be harmful during pregnancy and while breastfeeding. Patients should discuss any plans to become pregnant with their physician as a change in drug regimen may be required.

Also, patients should not take antacids containing magnesium or aluminum (such as Mylanta, Maalox, Amphogel) at the same time as they take mycophenolate because antacids can make this drug less effective. Tums (calcium carbonate) is okay to use because it has no effect on mycophenolate.
LHSC's Pharmacy provides more detailed information about CellCept.

Prednisone:
Prednisone continues to be an integral part of anti-rejection drug treatment. Although effective, it is associated with significant toxicity. Side effects, such as a tendency to glucose tolerance, osteoporosis, adrenal suppression, obesity, acne, edema, hypertension and increased susceptibility to infection, are not uncommon.

A trend in liver transplantation has been more rapid tapering of steroids or avoidance of steroids altogether. Currently, patients are discharged from hospital taking prednisone 20 mg/day. We recommend the following tapering schedule:

1-2 months	15 mg once a day
2-3 months	10 mg once a day
3-6 months	7.5 mg once a day
>6 months	0-5 mg once a day

Six months after transplant, patients who were not on prednisone preoperatively and have normal liver enzymes can have their dose withdrawn over several months. LHSC's Pharmacy provides more detailed information about prednisone.

Sirolimus (Rapamune®):
Sirolimus is usually taken once a day, preferably at the same time every day. Although structurally similar to Prograf, sirolimus possesses a different mechanism of action with different side effects. Nephrotoxicity,

commonly seen with calcineurin inhibitors, is rare. Similarly, sirolimus appears to be associated with a low risk of neurotoxicity, hypertension, and diabetes. However, several medications do not mix well with sirolimus, and they may affect the level of sirolimus. For example, drugs that are used to treat high cholesterol and triglycerides may become more potent when taken with sirolimus.

Common side effects include thrombocytopenia, leukopenia, proteinuria, hypertriglyceridemia, and hypercholesterolemia. All appear to be dose related and reversible with reduction or withdrawal of the drug. Complete blood counts should be monitored periodically, and the dosage reduced or drug stopped if platelets are <50 or the white cell count is <4.0. Hypercholesterolemia may respond to dose reduction or to lipid-lowering agents.

Given the different side effect profiles of the calcineurin inhibitors and sirolimus, combination therapy appears attractive. By administering sirolimus with a calcineurin inhibitor, both at reduced doses, effective immunosuppression can be achieved while reducing the risk of side effects from either drug.

The starting dose is usually 1-3 mg daily. This dose seldom requires adjustment. The half-life of sirolimus is very long compared to other immunosuppressive agents, making daily monitoring unnecessary. Monitoring may be as infrequent as once per month. The current recommendations for target trough serum levels are 5-10 ug/L (during the first month) and 1-5 ug/L (after the first month). LHSC's Pharmacy provides more detailed information about sirolimus.

Follow-up Care

Lab Monitoring and Clinic Visits:
Most patients returning to their home community initially require blood work and clinic visits once a week. This is decreased over time as their condition improves. We recommend the following schedule of blood taking and clinic visits if blood tests are stable:

Months 0-3:	Clinic visits - every 1-2 weeks
	Blood tests - every 1-2 weeks
Months 4-6:	Clinic visits – 1-2 months
	Blood tests - every 2- 3 weeks
Months 6-12:	Clinic visits - every 2-3 months
	Blood tests - monthly
> Month 12:	Clinic visits - every 6- 12 months
	Blood tests – monthly

Blood tests have been arranged by the LHSC transplant program at a laboratory convenient for the patient. The results of the following blood tests will be forwarded to you:

CBC, Platelets, INR
Sodium, Potassium, Chloride, Bicarbonate, Urea, Creatinine
Random Glucose, Total Bilirubin, Magnesium, ALT, AST, Alk. Phosphatase
Cyclosporine / Prograf/ Sirolimus levels

Contact with London Health Sciences Centre

The transplant group at London Health Sciences Centre, University Hospital continues to have an active interest in all transplant recipients. We are always available to act as consultants in patient care and **request that laboratory results be forwarded on a regular basis**. When a patient's condition warrants a liver biopsy, we would appreciate a copy of the pathology report, which can be sent to the Clinic.

LONDON HEALTH SCIENCES CENTRE, UNIVERSITY HOSPITAL

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Prograf: Drug Interactions

Effects	Known Interactions	Suspected Interactions
Drugs increasing the serum levels of Prograf	■ itraconazole ■ ketoconazole/fluconazole ■ erythromycin/clarithromycin ■ nefazadone ■ oral contraceptives ■ grapefruit juice ■ danazol ■ calcium-channel blockers; diltiazem, verapamil ■ boceprevir and telaprevir	■ cimeticline ■ chloroquine ■ dapsone ■ mefloquine ■ midazolom ■ omeprozole ■ ergotamine
Drugs decreasing the serum levels of Prograf	■ antacids or anticonvulsants ■ rifampin or isoniazid ■ octreotide	
Drugs causing additive nephrotoxicity	■ cyclosporine ■ amphotericin B ■ aminoglycosides ■ cisplatin	■ non-steroidal anti-inflammatory drugs ■ vancomycin ■ IV pentamidine ■ co-trimoxazole
Others	■ MMF	■ K+ sparing diuretics ■ digoxin ■ captopril ■ toxoids or vaccines ■ acyclovir

Cyclosporine: Drug Interactions

Effects	Known Interactions	Suspected Interactions
Drugs increasing the serum levels of cyclosporine	■ ketoconazole ■ fluconazole ■ itraconazole ■ tacrolimus ■ erythromycin ■ corticosteroids ■ oral contraceptives ■ norethisterone or danazol ■ doxycycline ■ metoclopramide ■ bromocriptine ■ calcium-channel blockers; diltiazem verapamil, nicardipine ■ propafenone ■ boceprevir and telaprevir	■ ranitidine/cimetidine ■ cephalosporins ■ thiazide diuretics ■ furosemide ■ androgenic steroids ■ acyclovir ■ warfarin
Drugs decreasing the serum levels of cyclosporine	■ phenytoin ■ phenobarbital ■ carbamazepine ■ rifampin ■ isoniazid ■ octreotide ■ ticlopidine	■ sulfinpyrazone
Drugs causing additive nephrotoxicity	■ amphotericin B ■ aminoglycosides ■ melphalan ■ co-trimoxazole ■ diclofenac ■ vancomycin ■ ciprofloxacin ■ colchicine	■ non-steroidal anti-inflammatory drugs
Alteration of immunosuppressive effect		■ propranolol ■ verapamil ■ etoposide
Interaction of immunosuppressive effect		■ disulfiram ■ chlorpropamide ■ metronidazole
Others	■ grapefruit juice	■ digoxin ■ captopril ■ toxoids or vaccines ■ lovastatin