New Zealand Liver Transplant Unit
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SHARED CARE GUIDE FOR PATIENTS UNDERGOING LIVER TRANSPLANTATION

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OBJECTIVES

1. To improve outcomes for all liver transplant recipients.
2. To optimise shared care of the liver transplant recipient by providing information for GPs and local hospitals regarding the care of the liver transplant recipients.
3. To define which aspects of care are the responsibility of the NZLTU and which are those of the GP and referring physician.
4. To improve communication between GP, local hospital and the NZLTU.
5. To provide specific pharmaceutical advice where appropriate.

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(a)INTRODUCTION

Liver transplantation is now accepted as a standard treatment for end stage liver disease (decompensated cirrhosis), small hepatocellular carcinoma and acute liver failure. The aim of transplantation is to return patients to a normal life without any limitations, but with the proviso that they will need to be on immunosuppressant treatment for the rest of their lives.

Results have improved steadily since the first transplant was performed in 1963, largely due to huge advances in immunosuppression, surgical techniques and intensive care. We would now expect >95% one-year survival and 87% five-year survival in patients who are transplanted at the NZLTU.

Many GPs and physicians may not be familiar with the potential problems associated with long-term immunosuppression. These include opportunistic infections (viral, bacterial, fungal and protozoal), EBV-related lymphoproliferative disease, increased risk of skin cancer, headaches, hypertension, obesity, diabetes, lipid disorders and renal dysfunction.

In addition, there are some difficulties specific to liver transplant recipients. Liver allograft dysfunction can result from either rejection, infection, technical problems with the liver graft (biliary and vascular), or recurrence of the primary disease in the graft. The cause of graft dysfunction may be difficult to distinguish.

The main reason for transfer of care back to the local physician is that most of the patients live a long way from Auckland City Hospital (ACH), the referring physician / gastroenterologist will have better knowledge of the patient's past history, family support and domestic conditions.

Most cases of acute liver failure are referred from intensive care units without ever seeing a local gastroenterologist or general physician. Under these circumstances, a local gastroenterologist or general physician will be identified and contacted by NZLTU to ensure that the patient has continuity of care when the patient returns home from Auckland.

At the point of discharge from hospital, the Discharge Summary will be sent to the GP and the designated local physician. Both will also receive all Transplant Clinic letters until the patient returns home at 6-12 weeks after transplant. The Transplant Coordinator will ensure that the patient has a scheduled appointment with the local physician within 2 weeks of returning home to ensure continuity of care.

In order to improve communication between NZLTU, the local physician and GP, we will include all the relevant telephone and fax numbers and the NZLTU email address at the end of this document. We hope for shared care arrangements between the NZLTU and the referring physician and GP to be in place at approximately one month post-transplant.

This document is to provide a guide for the referring physician and GPs to assist with and optimise the care of the liver transplant recipient in New Zealand.

(b)THE TRANSPLANT ASSESSMENT

Referrals to the New Zealand Liver Transplant Unit (NZLTU) for patients who need to be considered for liver transplantation from the patients Physician or via the Hepatocellular Carcinoma (HCC) Multidisciplinary Meeting (MDM) for patients should include:

- Medical / surgical history
- Investigations, imaging completed
- Social history
- Drug and alcohol history
- Support system

The Liver Transplant assessment occurs in Auckland over a week - Monday to Friday. The Liver Transplant Coordinator (LTC) will contact the patient to arrange the assessment usually as an outpatient. The patient will need to arrange their travel and accommodation through their local accommodation officer at their domicile DHB. It is essential a support person is present for the entire week. During this week, patients will receive an individualised timetable depending on their needs.

As a minimum requirement, patients will have appointments with the following:

- Duty Hepatologist
- Transplant Surgeon
- Transplant Coordinator
- Social worker
- Anaesthetist
- Dietician
- Physiotherapist

Some patients may need to have appointments with:

- Psychiatrist
- Dentist

All patients will need to have:

- Gastroscopy
- ECG
- Chest Xray
- Echocardiogram (LV function, Right heart pressures, valvular disease)
- Lung function
- Radiological imaging of their liver (CT, US, MRI)
- 24-hour urine collection (creatinine clearance and protein)

Some patients may need:

- MR STIR
- CT coronary angiogram
- CT chest
- Right heart catheter

(c)PRE-TRANSPLANT

Vaccinations:

The following vaccinations will be administered to the patient at the time the patient is listed for liver transplant:

- Prevenar 13 and Boostrix. Hepatitis A and Hepatitis B as required. The first dose is usually given by transplant coordinators with a follow up letter sent to GP to follow up with further vaccinations if required.

Blood tests:

These are required monthly to update the patients MELD score whilst on the waiting list. This should include FBC, U+E's, LFT's, INR.

If the patient has HCC, then AFP measurement at monthly interval.

Radiology:

- Ultrasound every 3 months looking for HCC and checking portal vein patency.
- CT or MRI every 3 months if the patient has known HCC,
- MRI of spine and CT chest every 12 months if the patient has known HCC

Patients to be reviewed at a minimum of 3-monthly intervals locally by referring specialist.

Please notify the NZLTU if the patient is admitted to hospital. This may lead to the patient being prioritised for transplant or suspended from the list, depending on the reason for the admission.

(d) POST-TRANSPLANT

Discharge from Hospital

Patients are usually discharged from hospital between 6 and 14 days post-liver transplantation. A full clinical summary will be sent out to all referring physicians and GPs within 48 hours of discharge.

Prior to discharge, each patient will be given a 'Transplant Diary' with information relating to complications post-transplant and the ability to record their daily medications. They will also be given a yellow medication card. Any alterations in drug therapy will be documented in both the diary and the yellow medication sheet. Each patient will be encouraged to wear a 'Medic Alert' bracelet, outlining that they are liver transplant recipients, the immunosuppressive drugs, drug allergies and any specific complications.

Patients who live in the Auckland region will be discharged directly home. Patients living outside Auckland will be provided with local accommodation until they return home 6-10 weeks post-transplant. Accommodation will also be provided for the identified caregiver during this period. This will be funded by the local DHB.

Outpatient Clinic

Initially, patients will be seen twice weekly for 3 weeks and then weekly for 4 weeks. By the time of discharge from NZLTU back to the referring physician, most patients will be seen fortnightly. Clinic visits usually continue at monthly intervals for a further 6 months and providing there are no complications, then 3-monthly thereafter. Diabetics will need more intensive follow-up.

On each clinic visit, all patients will be seen by either the Duty Hepatologist, Transplant Surgeon, Nurse Practitioner or the Transplant Co-ordinator.

What is done in the clinic?

A regular blood test is done prior to each clinic visit so that results are available for review. Blood tests should include Full Blood Count, INR (if on warfarin or if significant graft dysfunction), biochemistry profile (including U+E, Creatinine, glucose, albumin liver function tests (ALT, ALP, GGT and bilirubin) and AST. If the patient had hepatocellular carcinoma before transplant, serum AFP is measured. Whole blood tacrolimus, sirolimus or cyclosporin levels should be measured.

Each patient's weight and the blood pressure are measured. The abdomen is examined for tenderness, presence of masses, enlargement of the liver (which should feel normal in size). If recently transplanted, the scar is examined in detail.

A letter will be dictated each clinic visit documenting the latest blood results, current medications and a summary of the patient's clinical condition.

Return to Domicile DHB

When a patient is returning home, both the local physician and GP should have received:

- Discharge summaries
- Operation note
- Clinic letters
- Recent blood results

The patient will have an updated yellow medication card, a new blood form with copies to the GP and the local physician, and a prescription with current medications required.

If any further information is required or is missing, please contact the transplant coordinator who will provide it.

Once the patient is home, it is expected that the patient gets subsequent prescriptions from the GP or the referring physician.

Role of the Local or Referring Physician

Currently, the NZLTU is funded to provide care only for the first 12 weeks after transplant. If the patient lives outside the Auckland District Health Board catchment region, then the referring physician is expected to arrange patient long-term management following liver transplantation. The physician may wish to refer the patient to a colleague with more experience or interest in managing liver transplant recipients. This depends very much on whether the physician wants to manage the post-transplant patient, and will depend on previous experience, local facilities and distance from Auckland. Patients who live a long way from Auckland will need to see their local physician on a regular basis.

Please forward to NZLTU copies of all clinic letters and blood results. NZLTU would also appreciate hospital discharge summaries and notification of any death (expected or not).

The NZLTU would prefer to see all transplant recipients who are causing concern and may need tertiary input into ongoing management (e.g. lymphoma, biliary stricture). Non-urgent review can be provided at satellite clinics that the NZLTU conducts in Wellington, Christchurch and Dunedin. Urgent review will require referral to the duty NZLTU Duty Hepatologist at Auckland City Hospital.

Outpatient review can be arranged at the weekly Transplant Clinic. In patient review will require transfer to Ward 71 Auckland City Hospital. Transfer will need to be arranged through the referring DHB.

Clearly communication between the GP, local hospital and the transplant team are of greatest importance when patients are attending all three places.

Role of the General Practitioner

After the patient returns home it is essential that the GP remains involved with the patient's ongoing management, as the GP may be the first person contacted in an emergency. We therefore encourage the patients to continue to see their GP. Clearly the GP will be much more familiar with the patient, their previous illnesses, their social situation and the family, therefore for this reason we like to leave as much as possible of the general care of the patient to them. Also, many of the complications of transplantation (obesity, diabetes, and hypertension) may be best managed through primary care. Seasonal influenza vaccination will also be provided by the GP.

Medications

Immunosuppression

Most patients under the care of NZLTU are maintained on Tacrolimus monotherapy. Some patients at higher risk for either late rejection or recurrent/de novo autoimmune hepatitis are also maintained on small doses of Prednisone.

The following is a "guide only", for management of the care of the transplant recipient as the management is often multifactorial and complex.

(i) Tacrolimus (available in 0.5mg, 1mg and 5mg tablets)

Most patients start tacrolimus day 1 post-transplant. This is taken twice daily (12 hrs apart) usually in equal doses. The blood concentrations are measured as trough levels. Target trough tacrolimus levels aimed for over the first 12 months:

a. 1-8 weeks: 12-15µg/L
b. 8-24 weeks: 8-10 µg/L
c. 24 weeks onwards: 5-7 µg/

Factors to take into consideration when adjusting the dose are:

i. Is the level a true trough level?
ii. Is there evidence of toxicity – renal impairment, persistent tremor, headaches, hypertension?
iii. Is the lift graft function normal?
iv. Have there been previous rejection episodes and have any been steroid resistant (needing ATG or plasmapheresis).
v. Is the patient adherent (are levels fluctuating)?
vi. Is there any evidence of ongoing substance use?
vii. Is the patient taking any concomitant medicines which could increase tacrolimus levels (antifungals, macrolide antibiotics, protease inhibitors including ritonavir; calcium antagonists)?
viii. Is the patient taking any concomitant medicines which could decrease tacrolimus levels (anticonvulsants, anti-TB medication)?
ix. Does the patient have any gastrointestinal disorder that can reduce absorption (rare for tacrolimus)?

All changes to tacrolimus doses should be followed up with a repeat blood test the following week. Special Authority approval is required for tacrolimus, this is life long and done prior to the patients discharge post liver transplant.

Side effects: Common side effects include tremor, headaches and diarrhoea. Severe side effects include nephrotoxicity, altered conscious state (with mutism), and very occasionally fits. The drug is also diabetogenic in higher doses.

(ii) Prednisone

All patients are given 1g IV methylprednisolone at induction. Then from day 1, they are started on 20mg OD for 2 weeks. This is then reduced to 15mg OD, and then weaned fortnightly by 2.5mg until they have stopped this medication. Exceptions for this are patients transplanted for autoimmune hepatitis or who develop recurrent or de novo autoimmune hepatitis and patients at risk for late rejection. This includes all patients who have had steroid-resistant rejection requiring thymoglobulin and/or plasmapheresis. These patients usually remain on 5mg OD prednisone long term.

(iii) Mycophenolate Mofetil (MMF) (available in 250mg and 500mg tablets)

MMF is not a first line IS medication used in liver transplant patients. It is commonly started due to renal impairment. Tacrolimus levels can be run at a lower level when used in conjunction with MMF, however liver function tests need to be monitored carefully when lowering the tacrolimus dose.

a. On occasion, if renal impairment is severe and the patient has not had rejection, it is safe to stop Tacrolimus and have the patient on MMF + 10mg prednisone. This should be done with consultation with the duty hepatologists at the NZLTU and the patients graft function monitored **closely (weekly) for 8 weeks.**

Side effects from MMF are diarrhoea, nausea, vomiting, constipation, anorexia and pancytopenia. There are anecdotal reports of an increased risk of reactivation of viral infections such as CMV. See notes below relating to pregnancy (Page 20).

Monitoring levels: Monitoring levels of mycophenolate mofetil is not necessary or recommended.

(iii) Sirolimus: (available as 1mg and 2mg tablets or in 1mg/ml solution)

Sirolimus is a potent immunosuppressant with different mechanism and side-effect profile than cyclosporin or tacrolimus. It has no nephrotoxicity and therefore can be used as rescue therapy in patients who develop calcineurin inhibitor-induced nephrotoxicity. It is important to check that the patient has no significant proteinuria prior to starting Sirolimus, as proteinuria is a contraindication to Sirolimus. ~~-~~ Target trough levels during first 12 months post-transplant are 12-20 ng/ml and late post-transplant are 8-12 ng/ml.

Common side effects: Mouth ulcers, hypercholesteraemia (treat with statin); thrombocytopenia. Impaired wound healing is common due to anti-VEGF effect of sirolimus. Tmay occasionally result in wound dehiscence. These patients should be temporarily switched to low dose tacrolimus 7 days before and until the wound is well healed (for a minimum of 4 weeks after surgery).

Rare side effects: Interstitial pneumonitis.

The RESPECT Protocol

This is initiated as a renal sparing protocol for patients who are at risk for acute renal injury post-transplant, including the following:

(i) Emergency transplant for acute liver failure
(ii) Retransplant
(iii) Combined liver-kidney transplant
(iv) Pretransplant hepatorenal syndrome
(v) Renal impairment at the time of transplant
(vi) Intra-operative oliguria

Patients receive IV basiliximab 20 mg on day 0 and 5, start Mycophenolate Mofetil (MMF) and prednisone on Day 1. Tacrolimus is delayed until Day 5, initially aiming for lower levels (8-12µg/L). These patients will remain on this regime indefinitely depending on the recovery of their renal function. Tacrolimus levels can gradually reduce over time (dependent on incidences of rejection and remaining on MMF). These patients will be weaned off prednisone as per protocol (see above). If the renal function recovers and the patient is able to maintain adequate tacrolimus levels, then the MMF may be able to be stopped (always followed by close monitoring of the liver function).

How to treat late acute rejection

All patients with acute graft dysfunction should have an ultrasound to exclude biliary obstruction. They should then have a liver biopsy (covered by one dose of IV cefuroxime or amoxycillin/gentamicin). If the liver biopsy demonstrates histologic features of acute cellular rejection, then the following treatment should be considered:

(i) Minimal or Mild Rejection (BANFF Score 3 or 4): consider increase in tacrolimus aiming for a trough level of greater than 12ng/ml. If the graft dysfunction does not resolve, then biopsy should be repeated.
(ii) Mild or Moderate Rejection (BANFF Score ≥4): pulse steroid therapy: 1g IV methylprednisolone for 3 days, followed by 20mg prednisone OD, weaning thereafter by 5 mg per month.

It is important to monitor blood sugars regularly because hyperglycaemia is common and short acting insulin sliding scale may be required for a few days.

Important Drug Interactions

1. Tacrolimus, Cyclosporin and Sirolimus undergo extensive metabolism in the liver and any drug affecting the microsomal p450 oxidation system will alter their elimination and alter levels.

The following is a table of possible drug interactions:

Drugs that **REDUCE** blood levels. Increased dose required	Drugs that **INCREASE** blood levels. Reduce dose required
Rifampicin Carbamazepine Phenobarbitone Phenytoin Prednisone Sodium valproate	Sirolimus Amiodarone Diltiazem/Verapamil Chlorpromazine Erythromycin/Rothrixomycin Metoprolol Metronidazole Probenecid Warfarin Fluconazole/Ketaconazole/Itraconazole Ritonavir, HIV and HCV protease inhibitors

1. **Allopurinol** blocks the metabolism of azathioprine.

2. **Nephrotoxic drugs** such as NSAIDs and aminoglycosides increase nephrotoxicity of cyclosporine and Tacrolimus. In general, NSAIDs should not be given to these patients, although sulindac appears to be the one that interacts least.

3. **Potassium retaining diuretics** may exacerbate hyperkalaemia due to cyclosporine and tacrolimus.

Prophylactic Drugs

A number of these are given routinely post liver transplant.

a. **Anti-ulcer prophylaxis:** Omeprazole 40 mg/day for first 4 weeks only (unless other indication for long-term therapy such as gastroesophageal reflux, Barrett's)
b. **Anti-fungal prophylaxis:** Fluconazole 100mg/day for first 4 weeks only
c. Antiviral prophylaxis:
- Against CMV in high-risk patients (see below): Valganciclovir 900mg/day for first 12 weeks only
- Against genital Herpes in affected patients: Acyclovir 400mg/day life-long

Other drugs

a. Treating Hypertension

Definition of hypertension: Systolic BP > 160 ± diastolic BP > 90mmHg

Almost 50% of liver transplant recipients will develop de novo hypertension on tacrolimus or cyclosporine. If persistently elevated, then the following measures:

- Lifestyle modification: weight loss; limit salt intake
- Reduce tacrolimus dose if tough level is high

1st Line Drugs: Angiotensin Converting Enzyme Inhibitors (ACE-I)

(i) Cilazapril 1.25 mg mane, increase to 5 mg mane
(ii) Quinapril 10 mg mane, increase to 40 mg mane
(iii) If not controlled, add thiazide (cilazapril 5mg/hydrochlorothiazide 12.5mg)
Caution: renal dysfunction or hyperkalaemia

2nd Line Drugs: Angiotensin II Receptor Blockers (ARBs)

(i) Losartan 25 mg mane, increase to 50 mg mane
(ii) Candesartan 4 mg mane, increase to 40 mg mane
(iii) If not controlled, add thiazide (Losartan 50mg/hydrochlorothiazide 12.5mg)
Caution: renal dysfunction or hyperkalaemia

3rd Line Drugs: Calcium antagonists:

(i) Felodipine, Amlodipine
(ii) Caution with Diltiazem, Verapamil raise tacrolimus levels
S/E bradycardia, bronchospasm, Caution: diabetes

4th Line Drugs: Beta-blockers:

(i) Cardioselective: Metoprolol
(ii) Non-selective: Atenolol, nadolol
S/E bradycardia, bronchospasm, Caution: diabetes

b. **Diuretics:** Occasionally small doses of frusemide are needed for oedema, but these should be reduced and weaned off if possible. Spironolactone is voided because of risk of hyperkalaemia with tacrolimus

c. **Treatment of Osteoporosis:** Patients with cholestatic liver disease should receive calcium and vitamin D replacement. Severe osteoporosis (Z score >-2) should be treated appropriately with etidronate 400mg/day for 2 weeks cycling with Calcium 1g/day for 10 weeks. If osteoporotic fracture has been documented, then alendronate should be considered (needs Endocrinologist Special Authority). Patients can also be referred to Endocrinology for consideration of an annual Zoledronate infusion, if indicated.

d. Hepatitis B Antiviral Prophylaxis

(i) Following transplantation for acute, acute-on-chronic and chronic HBV

Tenofovir disoproxil is administered life-long from day of transplant. Those patients previously suppressed on entecavir will be switched to tenofovir at the time of listing.

The usual tenofovir dose is adjusted according to renal function (based on eGFR):

1. eGFR >50ml/day: 245 mg once daily
2. eGFR 30-49 ml/day: 245 mg every second day
3. eGFR 10-29ml/day: 245 mg twice weekly
4. eGFR <10ml/day: 245 mg once weekly after dialysis

This medication should NOT be stopped without discussion with the NZLTU.

Most patients transplanted for HBV prior to 2018 are participating in a long-term clinical trial of tenofovir alafenamide (TAF). This drug has no nephrotoxicity and the dose is 25mg/day with no dose adjustments required in patients with renal dysfunction.

Patients on tenofovir disoproxil who develop evidence of renal tubular leak (hypophosphatemia or Fanconi syndrome) should be switched to entecavir or if they have a history of lamivudine resistance a NPPA should be made for TAF.

(ii) Following transplantation of a liver from an anti-HBcore positive donor into an HBV naïve recipient

These patients are at risk for HBV reactivation at any time post-transplant because of the effects of immunosuppression on latent HBV within the liver allograft. This will be prevented by long-term antiviral therapy. Lamivudine was previously used, but entecavir or tenofovir can now be prescribed for these patients.

Late Complications after Liver Transplantation

Graft Dysfunction

All episodes of graft dysfunction are potentially serious. Graft dysfunction can be caused by many factors. Without appropriate investigation and management, it could cause irreversible graft injury resulting in liver failure, retransplantation, or death.

(i) **Hepatitic pattern of graft dysfunction:**

ALT and AST >2xULN, ALP and GGT <5x ULN, bilirubin N or increased.

This can be due to (in decreasing likelihood):

1. acute cellular rejection
2. recurrent or de novo viral infection
3. ischaemia from hepatic artery stricture or thrombosis
4. hepatic venous congestion from outflow obstruction
5. drug-induced liver injury

(ii) **Cholestatic pattern of graft dysfunction:**

ALT and AST <2xULN, ALP and GGT >5x ULN, bilirubin N or increased.

This can be due to (in decreasing likelihood):

1. biliary complications (stricture, leak, stones)
2. recurrent PBC or PSC
3. chronic allograft rejection

In all cases, the patient should be contacted to check for symptoms of cholangitis (fever, rigors, jaundice, itch associated with biliary complications) and history of new prescribed or over the counter medications or herbal medicines, and to check for adherence with immunosuppression. Patients (and their support) with pretransplant history of alcohol use disorder should be questioned about relapse.

Repeat liver function tests including immunosuppression levels. Also check creatinine, INR and platelets in case biopsy is required.

Patients with suspected cholangitis should be treated with antibiotics (if mild dysfunction and afebrile can treat as outpatient with oral quinolones; if severe dysfunction or febrile, treat as inpatient with IV cefuroxime or amoxycillin/gentamicin).

- An urgent Doppler Ultrasound of the liver should be performed to exclude biliary dilatation and hepatic artery thrombosis.

- If the intrahepatic bile ducts are dilated and the patient had duct-to-duct anastomosis at transplant, then needs an ERCP by an experienced operator.

- If the intrahepatic bile ducts are dilated and the patient had Roux loop anastomosis (biliary atresia, PSC, retransplant), then needs MRCP and discussion with NZLTU regarding need for PTC, locally or transfer to Auckland City Hospital.

Patients with graft dysfunction and Doppler evidence of either hepatic artery stenosis or thrombosis need urgent transfer to Auckland City Hospital.

Patients with graft dysfunction and normal intrahepatic bile ducts and a patent hepatic artery need an urgent liver biopsy to exclude acute rejection. Antibiotics should be administered immediately prior to the biopsy to prevent bacteraemia. Please discuss with NZLTU who may offer to review the biopsy and advise on treatment.

Rejection

Acute rejection occurs most commonly in the first 3 months. However, acute rejection may occur at any time especially if levels of immunosuppressive medication drop suddenly, either through misunderstanding, noncompliance, or reduced absorption (from vomiting or diarrhoea) or changes in drug bioavailability, produced by other drugs. Rejection is usually asymptomatic, although severe episodes may be accompanied with fever, malaise and jaundice. Biochemical graft dysfunction is primarily hepatitic (ALT and AST), with mild elevations in ALP and GGT. Clinical jaundice and itching are late symptoms of severe acute rejection or evolving chronic rejection. Liver biopsy is necessary to confirm the diagnosis of rejection prior to treatment (see Treatment of Rejection).

Please discuss all cases of biopsy-proven rejection with the NZLTU duty hepatologist. You should monitor the patient's graft function and tacrolimus levels closely during and after pulse steroid therapy. At the end of the 3 days of treatment, tacrolimus rough levels should be maintained between 10 and 15 ng/ml. If the AST does not normalise within a few days, then this usually reflects steroid-resistant rejection. This requires escalation of antirejection treatment and may necessitate transfer to Auckland City Hospital.

Infections

Infections are more common and potentially more severe in liver transplant recipients.

1. Bacterial Infections

These can occur at any time, but are particularly important in the first few months **when the patient is more heavily immunosuppressed**. Most common sites are chest or wound sepsis. In principle, bacteriological confirmation of the diagnosis should be arranged (sputum, wound swabs, MSU, stool±blood cultures**)**. Treatment with antibiotics should be started early and altered according to bacteriological results.

a) Chest Infection:

Although some patients with respiratory symptoms may have simple viral coryza and influenza, similar symptoms may herald a serious bacterial or viral pneumonia in the immunosuppressed patient, hence caution is needed. A chest X-ray should be performed if symptoms persist. Appropriate treatment for bacterial chest sepsis is Cefuroxime although Augmentin may be considered an alternative later than 8 weeks post**-**transplant.

Annual influenza vaccinations are recommended for all post liver transplant recipients

b) Wound Infection:

Drainage of a superficial wound collection**s** may be all that is required, although some patients may need to be treated with oral Flucloxacillin.

c) Clostridium difficle colitis:

This is a frequent cause of diarrhoea and/or fever following liver transplantation because of the immunosuppression and frequent use of antibiotics in the early post**-**transplant period. A stool specimen should be checked for *Clostridium difficle* toxin and standard therapy is 10 days oral Metronidazole (continued for at least 5 days after completion of other antibiotic therapy). Empirical treatment could be considered in any patient with previously confirmed *C.difficle* toxin, who represents with diarrhoea whilst awaiting the repeat stool toxin result. In patients with recurrent episodes of *C.difficle* colitis, faecal transplant could be considered.

d) Antibiotic Prophylaxis:

(i) Dental work greater than 8 weeks post-transplant (extractions, cleaning and scaling) should be covered with 2g oral Amoxycillin prophylaxis 1 hour prior to the procedure. If the patient has a penicillin allergy then 600mg oral clindamycin 1 hour prior to the procedure should be administered (as per heart foundation recommendations for dental procedure prophylaxis). If the patient is less than 8 weeks post-transplant, systemic antibiotics, i.e. Penicillin G 2mU and Gentamicin 160 mg (provided normal renal function) should be used.

(ii) All patients should receive prophylactic amoxycillin and gentamicin prior to ERCP or PTC procedures

(iii) Patients with Roux loop biliary anastomoses should receive prophylactic amoxycillin and gentamicin prior to liver biopsy or PTC.

In patients with renal impairment (eGFR <60 ml/min), amoxycillin and gentamicin should be substituted with amoxycillin and aztreonam or cefuroxime monotherapy.

2. Viral Infections

a) Cytomegalovirus (CMV):

Almost 70% of liver transplant candidates and organ donors will have latent CMV infection from childhood exposure. CMV is the most common viral infection following liver transplantation and is due to reactivation of latent infection in the seropositive recipients or de novo infection in the seronegative recipient of a liver from a seropositive donor (i.e. CMV mismatches). If no antiviral prophylaxis is given, CMV infection will occur in almost 50% of patients and CMV disease in almost 20% within the first 6 months. CMV disease can be either CMV Syndrome (fever unresponsive to antibiotics, malaise and neutropaenia) or tissue invasive disease (hepatitis, gastritis, colitis, retinitis, or pneumonitis).

Most cases of CMV disease occur in the following high-risk transplants:

1. Seronegative recipients of organs from seropositive donors (i.e. CMV mismatch)
2. Seropositive recipients who receive ATG for steroid-resistant rejection
3. Seropositive recipients who undergo emergency transplant for acute liver failure
4. Seropositive recipients who undergo retransplantation.

All high-risk patients now receive antiviral prophylaxis with oral valganciclovir for 12 weeks. Valganciclovir prophylaxis does not eradicate CMV disease, but rather delays the onset and attenuates the severity, thereby reducing the associated morbidity and mortality. As a result, most cases now occur later than 3 months after transplant i.e. after the patient has left Auckland and returned home. Therefore, it is important to consider CMV disease in any recipient who develops nonspecific symptoms and signs of CMV syndrome or specific symptoms and signs of tissue-invasive disease.

i. CMV syndrome is diagnosed by detection of significant viraemia (>3 log IU/ml). When assessing any herpes virus infection (CMV, EBV, HHV6, HHV7 and HHV8), always request viraemia quantitation to be performed in plasma NOT in whole blood. Herpes viruses exist in latent phase within PBMCs so will be detectable in whole blood in healthy patients without active infection.

ii. CMV tissue invasive disease is diagnosed by detection of significant viraemia together with histologic features of tissue injury plus evidence of inclusion bodies or immunostaining for immediate early antigen.

b) Epstein-Barr Virus (EBV):

Almost 90% of liver transplant candidates and organ donors will have latent EBV infection. In the 5% liver transplants that are EBV mismatches (i.e. seronegative recipients of a liver from a seropositive donor), all will develop de novo infection of whom more than half will develop EBV-related lymphoma. There is no accepted monitoring schedule for EBV mismatches. We currently recommend monthly EBV DNA quantitation in plasma. If EBV DNA climbs above 4 log IU/ml then reduction of immunosuppression should be considered after consultation with NZLTU. It is also important to include lymphoma in the differential diagnosis of any organ dysfunction.

c) Herpes simplex:

Patients with a history of labial cold sores (HSV Type 1) do not need antiviral prophylaxis. However, all patients with a history of genital herpes (HSV Type II) should receive lifelong valacyclovir 500mg once daily.

d) Varicella / Zoster:

Exposure of transplant recipients to individuals with chickenpox or shingles should usually be followed testing for HZV immunity. If testing is unavailable or if this confirms that the recipient is nonimmune, the recipient should receive Zoster Immune Globulin.

If the immune recipient develops reactivation (shingles) then he/she should be treated with high dose oral valacyclovir 1000 mg three times daily for seven days). Multidermatomal Zoster is life threatening and requires inpatient admission for intravenous acyclovir.

The current vaccine against both varicella (chickenpox) and zoster (shingles) is a live vaccine and is therefore contraindicated in immunosuppressed patients.

3. Fungal

Systemic fungal infection, although relatively rare, may affect chest or occasionally oesophagus or liver; it is always serious and always requires hospital admission. Local candidiasis of the mouth can be treated with oral Fluconazole.

Other Complications

1. Jaundice

Although patients with severe hyperbilirubinaemia on the waiting list (especially PBC, PSC, acute liver failure) may remain jaundiced for 1-2 weeks following transplant (longer if in renal failure), this will steadily resolve (more slowly in presence of severe renal dysfunction). Patients should not still be jaundiced when they return home. Recurrence of jaundice usually implies a significant problem with the graft – usually biliary, but occasionally late severe acute or chronic rejection. Patients who have rejection-related jaundice may rapidly progress to graft failure if diagnosis and appropriate management are delayed. Please discuss any patient with late onset jaundice with the NZLTU duty hepatologist.

2. Oedema and ascites

Patients may have persistent oedema and ascites (manifested as fluid losses through the operation drain sites) for some weeks after the transplant, until the neurohumoral mechanisms of the portal hypertension resolve completely. Oedema may be exacerbated by antihypertensive calcium antagonists, nifedipine and felodipine. Both usually resolve spontaneously but occasionally a small dose of diuretic is required. The late onset of oedema or ascites after transplant may suggest a mechanical problem with the graft - either obstructed hepatic venous outflow (thrombosis or stricture of either hepatic vein/IVC piggyback or IVC anastomosis) or recurrence of portal hypertension (either portal venous thrombosis or severe graft dysfunction).

3. Fever

Sepsis remains the leading cause of death in liver transplant recipients, therefore a temperature or chills and rigors at any time is a worrying sign in any immunosuppressed patient and can represent a systemic infection with bacteria, viruses or fungi. Patients are instructed to take their temperature daily, or if they feel unwell in the early post-transplant period, and to report any fever (≥38°C) immediately to their local physician or GP. Early assessment and discussion with one of the Liver Transplant team is essential (see contact numbers at end of this document). Treatment with appropriate antibiotics should be initiated as soon as possible as immunosuppressed patients often become septicaemic and deteriorate rapidly if antibiotic therapy is delayed.

(e) VACCINATIONS

The influenza vaccination should be offered to all immunosuppressed patients yearly

ALL live vaccinations are CONTRAINDICATED in transplant recipients including: measles, mumps, rubella, vaccinia, varicella, zoster, rotavirus Yellow Fever, Sabin polio vaccine (the Salk inactivated vaccine is safe), BCG (TB).

(f) PREGNANCY AND CONTRACEPTION

Although infertility is usual in liver transplant candidates with advanced liver disease, this rapidly reverses following transplantation. Both male and female transplant recipients can conceive within a few weeks of successful transplantation, so contraception should be considered in all men and women of childbearing potential. In general, patients should avoid pregnancy during the first year post-transplant. Barrier methods, low oestrogen contraceptive pills, or the Mirena IUCD are generally safe contraception for use in transplant recipients. However, other forms of IUCDs should be avoided due to the risk of infection.

Liver transplantation is not a contraindication to pregnancy in female liver transplant patients, although there is probably some increased risk of pre-eclampsia, low birth weight and prematurity. Prior to or during pregnancy immunosuppression may need to be altered and this needs careful discussion with the Transplant Team. All liver transplant recipients should be under High-Risk Obstetric care and close physician review for antenatal care and delivery. Breast feeding post-transplant is considered safe for the baby.

Mycophenolate Mofetil (MMF): This drug is teratogenic and men and women of child-bearing potential should not conceive whilst on this drug. MMF should either be stopped or replaced with azathioprine. Female recipients should use effective contraception during and for at least 12 weeks after discontinuation of MMF. Male recipients and/or their female partners of child-bearing potential should use effective contraception during treatment and for at least 90 days after discontinuation of treatment. Pregnancy exposure should be avoided (unless the maternal condition requires the drug).

Valganciclovir: This drug is teratogenic, and men and women of child-bearing potential should not conceive whilst on this drug and for at least 12 weeks after finishing.

(g) WELLNESS CHECKS

Skin Care

Patients who have received an organ transplant have a higher risk for developing skin cancers, up to 65 times that in non-transplant patients. Squamous cell carcinomas and melanomas are more aggressive and associated with poor prognosis, therefore assessment and management should be expedited in transplant recipients.

Preventative measures, early detection and rapid appropriate treatment of skin cancers are essential to minimise the harm caused by these cancers.

Marine Blue SPF 50 sunscreen (200g) is available to all immunocompromised patients on prescription. “Immunocompromised patient” must be written on prescription

Mammography

All women are screened as per the national guidelines. Those with a family history of breast cancer or over the age of 45 years should have yearly mammograms and regular breast examination otherwise.

Cervical smears

All women are screened as per the national guidelines. Those with an abnormal cervical smear results should be referred to the gynaecologist for urgent treatment.

Colonoscopy

All men and women over the age of 50 years are screened as per the national guidelines. It is recommended that patients who were transplanted for PSC and all those with inflammatory bowel disease have annual colonoscopies.

Upper GI Endoscopy in Patients with Barrett’s Oesophagus

Patients with Barrett’s Oesophagus should be offered screening according to published guidelines. Barrett’s segments less than 3 cm without intestinal metaplasia should have surveillance and biopsies every 2 years. Patients with long segment Barrett’s oesophagus should be referred for HALO ablation.

Patient should be on lifelong PPI.

If biopsies demonstrate moderate or severe dysplasia, then patient should be referred to the Upper GI/Gastro MDM regarding further endoscopic or surgical management.

If biopsies demonstrate low-grade dysplasia, then endoscopy and biopsies should be repeated and considered for endoscopic ablation. If ablation is not undertaken, 6-monthly surveillance is recommended.

(h)TRAVEL ADVICE

We encourage all liver transplant recipients to live life to the full once they have recovered from the operation. It is recommended that patients should not travel overseas for pleasure for at least the first 12 months. Travel to Australia or the Pacific Islands could be considered before then if urgent and the patient was well.

After 12 months, patients who are well with stable graft and renal function can travel to most countries. If travelling to Asia-Pacific, ensure that they receive appropriate vaccinations (but no live attenuated vaccines, such as yellow fever or polio). Patients should also have travel insurance, which covers their liver transplant and other pre-existing comorbidities. If the patient has trouble finding an insurer who will provide cover, they should contact the NZLTU transplant coordinator for advice. It is recommended that the patient travel with a current clinic letter and have plenty of medications (both in their luggage and on person).

(h) CANCER DATA

The NZLTU collects data on all recurrent and de novo malignancies in liver transplant recipients in order to better determine the risks and improve screening and management recommendations in our population. We would appreciate if the following information can be provided for all confirmed cancer cases.

Information required:

- Cancer type and site
- Date of diagnosis
- Mode of detection (screen-detected vs. incidental vs. symptomatic)
- Histology stage including site-specific information (e.g., Breslow's thickness for melanoma, ER/PR status for breast cancer)
- Type of treatment
- Outcome

This information is updated on the Australian Association of cancer registries by the New Zealand Liver transplant coordinators.

(i) PATIENT DEATH

The NZLTU collects survival data for the Ministry of Health and the Australian and New Zealand Liver Transplant Registry (ANZLTR). Please inform the transplant coordinator of any patient death, including the date and presumed cause.

(j) NZLTU CONTACT DETAILS

(i) Phone numbers:

- Liver Transplant Co-ordinators
  On call phone: 09 375 3434
  - Margaret Johnston
  - Barry Harrison
  - Fionna Miller
  - Vivienne Walker

- Hepatology Registrar
  - *021 416 720 or 021 412 015*
  - *021 884 631 (after hours and weekends)*

- On call Transplant Hepatologist
  - *Ed Gane: 021 548 371*
  - *David Orr: 021 548 372*
  - *Rachael Harry: 021 285 1969*
  - *Dominic Ray-Chaudhuri: 021 215 8474*

- Liver Unit Reception
  - *Christine Pandya: 09 307 4949 (ext. 22920)*

(ii) Email: aklivert@adhb.gov.nz

(iii) Fax: 09 375 4345