North of Tyne, Gateshead and North Cumbria Area Prescribing Committee

Shared Care Guidance for Immunosuppressive Treatment following Liver Transplantation in Adults

Updated June 2021

This guidance has been prepared and approved for use in North of Tyne, Gateshead and North Cumbria. It gives details of the responsibilities of GPs and specialist services in shared care arrangements and is intended to provide sufficient information to enable GPs to prescribe this treatment within the shared care arrangement. Secondary care will provide the initial three months of treatment, as agreed in the commissioning contract.

Further copies are available from:

NECS Medicines Optimisation Pharmacists	NECS Medicines Optimisation Team	T 01912172756
Medicines Management Unit, Freeman Hospital, Newcastle upon Tyne	Newcastle Upon Tyne Hospitals NHS Trust	T 0191 2231386

An electronic version of this document can also be viewed / downloaded from the North of Tyne Area Prescribing Committee's Website
http://www.northoftyneapc.nhs.uk

Approved on behalf of the	Name	Signature	Date
North of Tyne, Gateshead and North Cumbria APC Medicines Guidelines and Use Group			
North of Tyne, Gateshead and North Cumbria Area Prescribing Committee			

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North of Tyne Area, Gateshead and North Cumbria Prescribing Committee Shared Care Group

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An introduction to transplantation

The aim after liver transplantation is full rehabilitation, enabling an active and productive life. Long term prognosis is dependent on many factors, including rejection, infection and long term complications of immunosuppressive therapy. Long term follow up is therefore essential for the early detection and treatment of any or all of these possible complications. For this reason, all patients are closely supervised after discharge from hospital by the Transplant Unit, often in collaboration with local physicians.

Rejection is most likely to occur soon after the transplant, but it can occur at any time. Treatment of rejection is directed by the Transplant Unit and depends, in part, upon the time from transplantation. It usually entails high dose steroid administration as intravenous methyl prednisolone 1g daily for three days.

Post-transplant follow up.

Following successful transplantation, patients are seen in a specialist transplant clinic for the lifetime of their graft.

Routine Follow Up	**Bloods**	**Review**	
	ciclosporin/ tacrolimus/ sirolimus level		
	Full blood count Urea & electrolytes, glucose. liver function tests, bone chemistry, cholesterol	+ bloods	
2-4 weeks		weekly	
4-6 weeks		Weekly/fortnightly	
6-12 weeks		fortnightly	
3-6 months		monthly	
6-12 months		monthly	
1 year onward		3-6 Monthly	

Regular updates of progress will be forwarded from the transplant clinic detailing clinical status, medications and further follow-up arrangements.

What happens at a follow up appointment?

The focus of these early follow up appointments is on monitoring organ function and ensuring adequate immunosuppression. As the risk of acute rejection decreases, the intensity of immunosuppression is reduced to minimise adverse effects, in particular the nephrotoxicity of the calcineurin inhibitors ciclosporin and tacrolimus.

At the follow up appointment, regular checks are required to confirm the effectiveness of the immunosuppressive regime in individual patients.

At a follow visit patients can expect:

- Measurement of weight and blood pressure
- To see a SpR or consultant.
- Review all medications, initiation of changes including prophylaxis against opportunistic infections, and of long term comorbidities..
- Measurement of serum creatinine, electrolytes, LFT, FBC, random glucose and cholesterol, and trough levels of Ciclosporin, Tacrolimus and/or Sirolimus.
- Other assessments of transplant patients with intercurrent illnesses will depend on clinical requirement.

Following the clinic visit:

- Blood results will be reviewed by a doctor.
- Any abnormal results requiring action, or treatment changes, will be communicated to the patient by telephone, letter, or at a new appointment.
- A letter will be sent to the patient's GP documenting any changes or recommendations.
- Any change initiated in the dosage of the medication at the hospital visit will be written on the patient's drug record chart and communicated to the general practitioner.

The Newcastle protocol

All patients who have a functioning transplant will require immunosuppressive therapy for life. The six drugs presently in use are prednisolone, ciclosporin, tacrolimus, mycophenolate mofetil, azathioprine and sirolimus. These drugs are most frequently used in the following regimes:

Ciclosporin/ Tacrolimus +/- Prednisolone +/- Azathioprine/ Mycophenolate +/- Sirolimus.

When compared with ciclosporin, tacrolimus is associated with less pronounced adverse effects, and fewer cosmetic side effects.

Drug dosing and monitoring

Most episodes of acute rejection occur in the first few months following transplantation, thus target drug levels are highest in months 1 to 6. As the risk of acute rejection declines, target drug levels are reduced in order to minimise side effects whilst maintaining adequate immunosuppression

There are many important drug reactions. The most important are listed in the Shared Care Guideline for each drug, but great care is needed when prescribing for these patients.

Prophylactic Treatment

A number of drugs are given prophylactically, particularly during the first three months after transplantation.

Omeprazole Or Lansoprazole	20mg od 30mg od	Whilst on steroids (risk of peptic ulceration) i.e. Prednisolone >10mg.
Co-trimoxazole	480mg daily	For 3 months post transplantation or until Prednisolone < 10mg
Aciclovir	200mg tds	Prophylaxis for herpes simplex for a period of three months or until Prednisolone < 10mg
Valganciclovir	Dose dependent on renal function	Prophylaxis against CMV for 90 days. (Only for D+ R).

Other complications

Infection

Vigilance is essential and patients should report and discuss any fever with the Transplant Unit. The policy used in Newcastle upon Tyne Hospitals states not to treat infection blindly before initiating microbiological investigation. All vaccinations should be kept up to date, and *live* vaccinations (eg. oral Polio) should not be given. When patients are travelling abroad, appropriate vaccinations and antimalarial therapy should be administered (check with the Transplant Unit).

Susceptibility to infection (bacteria, viral, fungal and protozoal is increased in patients receiving immunosuppression therapy.

Anti-infectives

Any pyrexia of unknown origin in a transplant patient may be potentially serious and should be referred to the transplant unit immediately for evaluation.

Antibiotics

The following antibiotics can be prescribed when clinically appropriate:

i. Penicillins - safe
ii. Cephalosporins - safe
iii. Co-trimoxazole - safe
iv. Quinolones e.g. Ciprofloxacin - safe, but dose may have to be reduced.
v. Erythromycin, clarithromycin and azithromycin should in general be avoided, or only prescribed in consultation with the Transplant Unit, as they interact with tacrolimus and ciclosporin.

Viral Infections

Inhibition of T cell activity by immunosuppressive therapy particularly predisposes to TB, viral infections such as VZV, EBV and CMV, and fungal infections. (Pneumocystis carinii is the most important in the UK).

Cytomegalovirus- is common in the first three months post-transplant. Acute CMV infection/re-activation is treated with oral valganciclovir or intravenous ganciclovir.

Herpes infection of the nose and mouth is common and is treated with oral and topical acyclovir. Zoster/varicella infection may be more serious and require IV aciclovir.

Genital herpes and shingles are best treated by both oral and systemic acyclovir in standard doses (adjusted for renal function). This therapy should be started as soon as possible.

Hypertension is very common.

- Amlodipine and/or and ACE inhibitor used most commonly as these reduce nephrotoxicity.
- Diuretics are necessary in some patients for fluid retention. A loop diuretic such as furosemide is usual, and potassium-retaining diuretics should be avoided. Replacement potassium as Slow K is rarely necessary.

Hyperglycaemia has been observed in some patients on tacrolimus, and is exacerbated by concomitant steroid immunosuppression. It may require treatment with oral agents or insulin. Hyperglycaemia usually responds to careful dose reduction or replacing tacrolimus with an alternative agent.

Tremor, paraesthesia and headaches are the most common side effects of tacrolimus and ciclosporin, but only occasionally severe enough to warrant dose reduction.

Osteoporosis

Bone Disease All patients with abnormal pre-transplant bone densitometry will be followed up and the majority will receive oral bi-phosphonates.

Gout- If allopurinol is required for patient taking azathioprine, please discuss this with the Transplant Unit first as this potentiates azathioprine, and would require the azathioprine dose to be reduced to one quarter of its original dose.

It is imperative to notify the transplant unit before prescribing any medication to these patients.

1. Many drugs alter the metabolism of ciclosporin / tacrolimus resulting in elevated or depressed levels.

2. Other drugs may worsen nephrotoxicity;

- Non-steroidal anti-inflammatory agents should never be prescribed without prior consultation.
- Potassium sparing diuretics (amiloride, spironolactone, triamterene) are relatively contraindicated as potassium retention is a feature of ciclosporin / tacrolimus therapy.

General information

Cervical smears Female patients are advised to have an annual cervical smear irrespective of age.

Contraception Following transplantation fertility may return. Barrier methods and low dose oral contraceptives are recommended (not IUDs due to the risk of infection). Oral contraceptives use should be discussed with the Transplant Unit as these may also be contra-indicated in some patients.

Coping with Transplantation While the majority of patients cope admirably following transplantation, some have psychological difficulties.

There are three areas which may give rise to problems:

- Accepting that they now have a liver from someone who died to enable them to live.
- The relationship between the patient and the carer (usually spouse), which after the first few weeks is transformed if the patient is healthy again; some patients remain (unnecessarily) dependent on the carer, or alternatively the carer continues to dominate against the wishes of the patient. This is a very complex situation and may need professional help.
- The relationship between the patient and his/her peers in the community; many patients hate being treated as a celebrity or oddity and this also includes local medical staff.

Diet - After a successful transplant there are usually no dietary restrictions and patients are encouraged to eat a normal healthy, high fibre, low fat and sugar diet. However, up to 30% of liver transplant recipients gain significant weight and become obese. Obesity should be treated with regular lifestyle advice.

Chronic Hepatitis E is increasingly being seen in transplant recipients and can cause progressive liver fibrosis. The main source of hepatitis E is from undercooked pork. Patients should be counselled to ensure that all meat is adequately cooked, particularly processed products, such as sausages. The consumption of raw meat should be avoided.

Holidays - Transplant patients are advised to avoid local water, salads, ice cream and ice cubes when travelling abroad. A good intake of bottled water is advised. Recipients should take sufficient medication and a supply of anti-diarrhoeal treatment is advised. In addition it is often useful to carry a covering letter regarding their condition and to ensure that their insurance is adequate.

Malaria prophylaxis; Potential significant problems with drug toxicity and renal impairment (See BNF) so patients need individual advice and consultation.

Returning to work - As mentioned initially, the aim is for the patient to return to a full and productive life. Restrictions are few, and usually identified by commonsense. One important restriction is to avoid obvious sources of infection; in the first twelve weeks after transplantation patients are advised against using public transport and to avoid crowds. Returning to work is particularly encouraged if appropriate. If unable to do so on clinical grounds, there are benefits available from the Department of Work and Pensions and our social worker would be pleased to explain these to the patient. Certain occupations are not suitable. Normal driving is allowed 12 weeks after transplant; patients are encouraged to notify their insurance company to avoid complications in the event of a claim.

Other advice given is the same as that given to all patients, namely: regular physical exercise, abstinence from cigarette smoking, maintenance of ideal body weight.

Immunosuppressive Therapy

In the majority of cases this comprises of a cocktail of 'triple therapy', that includes three different types of drug are given concomitantly.
Doses of these medicines are adjusted by Transplant Unit. Dose changes are conveyed directly to the patient.

Responsibility for monitoring these medications and dose adjustment lie wholly with the Transplant Unit.

- It is expected that GPs supply these medicines, and this is far more convenient for the patients, particularly when visits to the Transplant Unit are less frequent.
- Repatriation of immunosuppressant prescribing for liver transplants is being planned however the timescales have not yet been agreed. It is absolutely essential that GPs continue to supply the immunosuppressant medications until formally notified by the Transplant Unit that the patient has been repatriated.
- Adjustment of the doses of these potentially toxic drugs is made according to:
    - rejection status
    - serum tacrolimus levels
    - renal and hepatic function and
    - haematological variables.

This explains the need for regular blood tests and the general practitioner may be invited to participate in this aspect of long term surveillance by arranging local facilities for measuring full blood count, urea, creatinine and electrolytes, glucose, and liver function tests, together with collecting and posting samples for ciclosporin / tacrolimus levels to Newcastle. This is particularly important to patients who live a long way away from Newcastle.

In the vast majority of patients ciclosporin / tacrolimus is for life and should never be stopped.

Ciclosporin Shared Care Guideline

Introduction

Ciclosporin has been used as a component of immunosuppressive therapy to prevent rejection of solid organ transplants since 1984. It is usually given in combination with an antiproliferative agent (azathioprine or mycophenolate mofetil) and prednisolone. Ciclosporin, and the newer drug, tacrolimus, are inhibitors of the enzyme calcineurin. Calcineurin inhibition suppresses T lymphocyte activation, which not only inhibits allograft rejection but also the T cell response to infection. Generic preparations of ciclosporin are now available and there may be significant variation in bioavailability between brands, therefore it is essential that these are prescribed using the brand name. Until further experience with the generic preparations is gained, only the Neoral® brand will be used in adult liver transplant recipients.

Responsibilities of the Transplant Unit

- Request participation in a Shared Care arrangement from the patients GP when the patient's treatment has been established and a Shared Care arrangement is clinically appropriate.
- Initiation of ciclosporin (Neoral®) therapy and dose titration and modification.
- Arrangements of all ongoing monitoring and responsibility for review of blood tests.
- Communication with GP of significant changes in ciclosporin dosage. Provision of information to patients regarding ciclosporin and monitoring.

Responsibilities of GP

- To contact the Transplant Unit to confirm that he/she will accept the shared care arrangement or not, within 28 days of receiving the request.
- Prescription of ciclosporin using the, correct, brand name, according to dose directed by the Transplant Unit.
- Communicate with Transplant Unit regarding any problems / compliance issues.
- Pneumococcal and annual influenza vaccinations are recommended for patients on immunosuppression therapy. **Avoid live vaccinations e.g. yellow fever, BCG, rubella, oral typhoid or polio.**
- **Avoid concomitant prescription of medications that interact with ciclosporin (see BNF Appendix 1).**
- Communication with the Transplant Unit should the patient develop intercurrent illness.

Information regarding ciclosporin

Indication	Liver transplantation.
Formulations and strengths available	Neoral® Microemulsion soft gel capsules, 10, 25, 50 and 100mg. Also available as a liquid at 100mg/ml
Cost	https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff
Dose	1-2mg/kg daily in two divided doses. Maintenance dose determined by trough (pre-dose) measurement of whole blood ciclosporin level. Target level varies according to the time since transplant.
Usual dose range	Related to ciclosporin blood level and time from transplant. 50mg bd up to 300mg bd.
Likely duration of treatment	Lifelong unless changed to an alternative by transplant unit.
Contraindications	Known hypersensitivity to ciclosporin
Warnings	Breast feeding is contraindicated. May be used during planned pregnancy under specialist advice. **Avoid all live vaccines (e.g. yellow fever, BCG, rubella and MMR).**
Side Effects (Full list in BNF)	Nephrotoxicity, Metabolic: hypertension, hyperlipidaemia, and hyperuricaemia. Cosmetic: hiruitism, gingival hypertrophy. Neurological: tremor, dysaethesia, rarely peripheral neuropathy. Increased susceptibility to infection. Increased risk of malignancy.
Drug Interactions (Full list in BNF)	**Ciclosporin metabolism is inhibited (and toxicity enhanced) by:** Macrolide antibiotics (erythromycin, clarithromycin & azithromycin) Azole antifungal drugs (fluconazole, itraconazole, clotrimazole) Calcium antagonists (diltiazem, verapamil & lercanidipine – less so other dihydropyridine drugs) Grapefruit juice **Ciclosporin metabolism is induced (and efficacy reduced) by:** Anticonvulsants (carbamazepine, phenytoin & phenobarbitone) Some antibiotics (rifampicin & rifabutin) St Johns Wort **Nephrotoxicity enhanced by all NSAIDs & sirolimus.**
Monitoring	Local blood tests requested in some patients; results to transplant unit who will assess results. **Dose modified by Transplant Unit only.**

Tacrolimus Shared Care Guideline

Introduction

Tacrolimus, like ciclosporin, is a calcineurin inhibitor. It is probably better at preventing acute injection than ciclosporin, although there is no evidence that tacrolimus improves long term graft survival. Both drugs are nephrotoxic. However, tacrolimus lacks the cosmetic side effects of ciclosporin, and may cause less hypertension and hyperlipidaemia. In contrast, post-transplant diabetes is more common with tacrolimus. Like ciclosporin, it is usually prescribed with an anti-proliferative agent (azathioprine or MMF) and prednisolone. Modified release tacrolimus (Advagraf® or Evarasus®) is prescribed for some patients who demonstrate compliance problems with the twice daily preparations. Generic preparations of tacrolimus are now available and there may be significant variation in bioavailability between brands. Therefore it is essential that these are prescribed using the brand name, this also avoids confusion between the twice daily and once daily preparations. New patients will usually be initiated on Adoport®.

Responsibility of Transplant Unit

- Request participation in a Shared Care arrangement from the patient's GP when the patient's treatment has been established and a Shared Care arrangement is clinically appropriate.
- Initiation of tacrolimus (usually Adoport®) therapy and dose titration and modification.
- Arrangements for all ongoing monitoring and responsibility for review of blood tests.
- Communication with GPs as to changes in tacrolimus dosage. Provision of information to patients regarding tacrolimus and monitoring.
- Provision of information to patients regarding tacrolimus and its monitoring.

Responsibilities of GP

- To contact the Transplant Unit that he/she will accept the Shared Care arrangement or not within 28 days of receiving the request.
- Prescription of tacrolimus using the, correct, brand name, according to dose directed by the Transplant Unit.
- Communicate with Transplant Unit regarding any problems / compliance issues.
- Pneumococcal and annual influenza vaccinations are recommended for patients on immunosuppression therapy. **Avoid live vaccinations e.g. yellow fever, BCG, rubella, oral typhoid or polio.**
- **Avoid concomitant prescription of medications that interact with tacrolimus (see BNF Appendix 1)**.
- Communication with the Transplant Unit should the patient develop intercurrent illness.

Information regarding Tacrolimus®

Indication	Liver transplantation.
Formulation and strengths available	Prograf® capsules 0.5mg, 1mg & 5mg Adoport® capsules 0.5mg, 0.75mg, 1mg & 5mg Advagraf® prolonged release capsules, 0.5mg, 1mg, 3mg, 5mg (only for use where specifically approved) and Envarsus® sustained release tablets, 0.75mg, 1mg & 4mg.
Cost - Prograf®	https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff
Cost - Adoport®	
Cost - Advagraf®	
Cost - Envarsus®	
Likely duration of action	Lifelong unless changed to an alternative by transplant unit.
Contraindications	Known hypersensitivity to tacrolimus
Warnings	Breast feeding is contraindicated. May be used during planned pregnancy under specialist. **Avoid all live vaccines (e.g. yellow fever, BCG, rubella, oral typhoid (rarely prescribed).**
Side Effects (Full list in BNF)	Nephrotoxicity Metabolic: hypertension, hyperlipidaemia, and hyperuricaemia. Cosmetic: hiruitism, gingival hypertrophy. Neurological: tremor, dyaesthesiae, rarely peripheral neuropathy Increased susceptibility to infection Increased risk of malignancy
Drug Interactions (Full list in BNF)	**Numerous:** including aminoglycosides, rifampicin, macrolides, trimethoprim, ibuprofen, diuretics. See BNF for longer list. Caution with NSAIDs, Grapefruit juice (increased tacrolimus levels). Please discuss concomitant prescribing with the transplant unit.
Monitoring frequency	Local blood tests requested in some patients; results to transplant unit who will assess results. **Dose modified by Transplant Unit only.** Monitoring frequency as directed by Transplant Unit.

Sirolimus Shared Care Guideline

Introduction

Sirolimus (Rapamune®) is an anti-proliferative, and acts by blocking the cellular response to cytokines and growth factors that signal through cell surface receptors. Sirolimus is equally effective at blocking the proliferation of immune cells (such as T lymphocytes) and non-immune cells. The latter effects include inhibition of wound healing, and possibly inhibition of tumour growth. For this reason, sirolimus may be less likely to cause malignancy than other immunosuppressive drugs. Unlike calcineurin inhibitors, sirolimus is not nephrotoxic, although does seem to enhance ciclosporin nephrotoxicity when both drugs are administered simultaneously. The product licence stipulates initial use of sirolimus in combination with ciclosporin or corticosteroids, but that ciclosporin be withdrawn 3 months following transplantation to avoid nephrotoxicity.

Responsibility of Transplant Unit

- Request participation in a shared care arrangement from the patient's GP when the patient's treatment has been established and a shared care arrangement is clinically appropriate.
- Arrangements for all ongoing monitoring and responsibility for review of blood tests.
- Communication with GPs as to changes in tacrolimus dosage.
- Provision of information to patients regarding sirolimus and its monitoring.

Responsibilities of GP

- To contact the Transplant Unit that he/she will accept the Shared Care arrangement or not within 28 days of receiving the request.
- Prescription of sirolimus (Rapamune®) according to dose directed by the Transplant Unit.
- Communicate with the Transplant Unit regarding any problems / compliance issues.
- Pneumococcal and annual influenza vaccinations are recommended for patients on immunosuppression therapy. **Avoid all live vaccinations e.g. Yellow fever, BCG, rubella, oral typhoid or polio.**
- **Avoid concomitant prescription of medications that interact with sirolimus (See BNF Appendix 1).**
- Communication with the Transplant Unit should the patient develop intercurrent illness.

Information regarding sirolimus

Indication	Liver transplantation.
Formulations and strengths available	Rapamune® Tablets 1 & 2mg Also available as a liquid at 1mg/ml.
Cost	https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff
Dose	1-5mg daily in one dose usually at midday
Usual dose range	Related to sirolimus blood level and time from transplant
Likely duration of action	**Lifelong unless changed to an alternative by transplant unit.**
Contraindications	Known hypersensitivity to sirolimus Pregnancy and breast feeding.
Warnings	Breast feeding is contraindicated. May be used during planned pregnancy under specialist. **Avoid all live vaccines (e.g. yellow fever, BCG, rubella, oral typhoid (rarely prescribed), MMR and live (oral) polio.** Inactivated polio vaccine may be used.
Side Effects (Full list in BNF)	Metabolic: hyperlipidaemia Haematologic: thrombocytopenia, anaemia and leucopenia Impaired wound healing Pneumonitis Increased susceptibility to infection Increased risk of malignancy
Drug Interactions (Full list in BNF)	**Sirolimus metabolism is inhibited (and toxicity enhanced) by:** Macrolide antibiotics (erythromycin, clarithromycin & azithromycin) Azole antifungal drugs (fluconazole, itraconazole, clotrimazole) Calcium antagonists (diltiazem, verapamil & lercanidipine – less so other dihydropyridine drugs) Grapefruit juice **Sirolimus metabolism is induced (and efficacy reduced) by:** Anticonvulsants (carbamazepine, phenytoin and phenobarbitone) Some antibiotics (rifampicin & rifabutin) St John's Wort
Monitoring	Local blood tests requested in some patients; results to transplant unit who will assess results. **Dose modified by Transplant Unit only.** Monitoring frequency as directed by Transplant Unit.

Mycophenolate Mofetil (MMF) Shared care Guideline

Introduction

MMF blocks both T and B lymphocyte proliferation by inhibiting purine nucleotide synthesis. Most cell types can synthesise purines using either a *de novo* or a scavenger pathway. MMF inhibits the rate limiting enzyme of this pathway (inosine monophosphate dehyrogenase- IMPDH), and for this reason it is a relatively specific immunosuppressive drug. Other bone marrow-derived cells are also susceptible to MMF, and anaemia, neutropenia and thrombocytopenia are common side effects.

MMF is a pro drug, and rapidly metabolised to the active compound mycophenolic acid (MPA) in the liver. MPA is excreted in bile, and undergoes entero-hepatic recirculation. As a result, the concentration of MPA in the intestinal lumen is high. This accounts for diarrhoea, which is the other important side effect of MMF.

Responsibility of Transplant Unit

- Request participation in a shared care arrangement from the patient's GP when the patient's treatment has been established and a shared care arrangement is clinically appropriate.
- Arrangements for all ongoing monitoring and responsibility for review of blood tests.
- Communication with GPs as to changes in mycophenolate dosage.
- Provision of information to patients regarding mycophenolate and its monitoring.

Responsibilities of GP

- To contact the Transplant Unit to confirm that he/she will accept the shared care arrangement or not within 28 days of receiving the request.
- Prescription of mycophenolate according to dose directed by Transplant Unit. Communicate with the Transplant Unit regarding any problems / compliance issues.
- Pneumococcal and annual influenza vaccinations are recommended for patients on immunosuppression therapy. **Avoid live vaccinations e.g. yellow fever, BCG, rubella, oral typhoid or polio.**
- **Avoid concomitant prescription of medicines that interact with MMF (See BNF Appendix 1)**.
- Communication with the Transplant Unit should the patient develop intercurrent illness.

Information regarding Mycophenolate Mofetil and Mycophenolic acid (Myfortic®)

Indication	Liver transplantation
Formulation and strengths available	250mg capsules & 500mg tablets. Oral suspension 1000mg / 5ml Also available as **mycophenolic acid (Myfortic)**. 720mg Myfortic is equivalent to 1000mg mycophenolate mofetil
Cost	https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff
Usual dose range	250-1500mg orally twice daily, Myfortic® 180-1080mg twice daily Patients taking tacrolimus or sirolimus may need lower MMF dose than those on ciclosporin.
Likely duration of action	Lifelong unless changed to an alternative by Transplant Unit.
Contraindications	Serious active gastrointestinal disease, patients at risk of GI bleeds or ulcers. Known hypersensitivity to Mycophenolic acid, Pregnancy and breast feeding.
Warnings	Elderly, children (higher risks of side effects in both). Active gastro-intestinal disease. **Avoid all live vaccines (e.g. yellow fever, BCG, rubella, oral typhoid (rarely prescribed), MMR and live (oral) polio.**
Side Effects (Full list in BNF)	Myelosuppression, gastro-intestinal toxicity, particularly diarrhoea. Increased susceptibility to infection. Increased risk of malignancy.
Drug Interactions (Full list in BNF)	Antacids and colestyramine reduce MMF absorption. Aciclovir and valganciclovir may increase risk of myelosuppression; plasma levels of aciclovir and valganciclovir increased by MMF. May also interact with theophylline, phenytoin, probenecid and aspirin. Please discuss concomitant prescribing with Transplant Unit
Monitoring	Local blood tests requested in some patients: results to Transplant Unit who will assess results. **Dose modified by Transplant Unit only.** Monitoring frequency as directed by Transplant Unit.

Azathioprine Shared Care Guideline

Introduction

Azathioprine, like MMF it is an anti-proliferative agent that acts by interfering with purine nucleotides. Azathioprine is metabolised to 6-thioguanine, which blocks DNA synthesis. Unlike MMF, this effect is non-specific and any proliferating cell type will be affected (see list of side effects below).

Azathioprine is usually used as part of triple immunosuppression in conjunction with a calcineurin inhibitor (ciclosporin or tacrolimus) and steroids. MMF is often substituted for azathioprine to allow for calcineurin inhibitor dose reduction.

Responsibility of Transplant Unit

- Request participation in a shared care arrangement from the patient's GP when the patient's treatment has been established and a shared care arrangement is clinically appropriate.
- Arrangements for all ongoing monitoring and responsibility for review of blood tests.
- Communication with GPs as to changes in azathioprine dosage.
- Provision of information to patients regarding azathioprine and its monitoring.

Responsibilities of GP

- To contact the Transplant Unit to confirm that he/she will accept the shared care arrangement or not within 28 days of receiving the request.
- Prescription of azathioprine according to dose directed by Transplant Unit.
- Communicate with the Transplant Unit regarding any problems / compliance issues.
- Pneumococcal and annual influenza vaccinations are recommended for patients on immunosuppression therapy. **Avoid live vaccinations e.g. yellow fever, BCG, rubella, oral typhoid or polio.**
- **Avoid concomitant prescription of medicines that interact with azathioprine (See BNF Appendix 1)**.
- Communication with the Transplant Unit should the patient develop intercurrent illness.

Information regarding Azathioprine

Indication	Liver transplantation
Formulations and strengths available	25mg & 50mg tablets
Cost	https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff
Dose	Initial dose 1.5mg/kg
Usual dose range	25mg to 150mg, in single daily dose
Likely duration of action	Lifelong unless changed to an alternative by Transplant Unit.
Contraindications	Known hypersensitivity to azathioprine or 6-mercaptopurine.
Warnings	Pregnancy and breast feeding. Azathioprine may be used during planned pregnancy under specialist advice. **Avoid all live vaccines** (e.g. yellow fever, BCG, rubella, oral typhoid (rarely prescribed), MMR and live (oral) polio. Inactivated polio vaccine may be used.
Side Effects (Full list in BNF)	Myelosuppression, hepatitis, pneumonitis, increased susceptibility to infection, increased risk of malignancy.
Drug Interactions (Full list in BNF)	**Dangerous interaction with allopurinol** Allopurinol inhibits azathioprine metabolism, leading to the accumulation of active metabolites and profound myelosuppression. In transplant patients requiring allopurinol treatment, azathioprine dose should be reduced to one quarter.
Monitoring	Local blood tests requested in some patients: results to Transplant Unit who will assess results. **Dose modified by Transplant Unit only.** Monitoring frequency as directed by Transplant Unit.

Prednisolone Shared Care Guideline

Introduction

Corticosteroids, like azathioprine, have been used as a component of immunosuppressive therapy to prevent allograft rejection since the first successful renal transplants in the 1960s. They act to inhibit the alloimmune response at multiple levels, but are relatively weak in comparison to the other immunosuppressive drugs in current use.

The side effects of long term corticosteroid use are well known (see below) and are the cause of considerable morbidity in transplant recipients. Modern immunosuppressive protocols aim to minimise corticosteroid exposure, and there is increasing evidence that steroids can be omitted completely from regimens including the potent drugs tacrolimus and MMF.

Responsibility of Transplant Unit

- Request participation in a shared care arrangement from the patient's GP when the patient's treatment has been established and a shared care arrangement is clinically appropriate.
- Arrangements for all ongoing monitoring and responsibility for review of blood tests
- To ensure that bone densitometry is performed at one year following transplantation where this is clinically appropriate.
- Communication with GPs as to changes in prednisolone dosage.
- Provision of information to patients regarding prednisolone and monitoring.

Responsibilities of GP

- To contact the Transplant Unit that he/she will accept the Shared Care arrangement or not within 28 days of receiving the request.
- Prescription of prednisolone according to dose directed by the Transplant Unit.
- Communicate with the Transplant Unit regarding any problems / compliance issues.
- Pneumococcal and annual influenza vaccinations are recommended for patients on immunosuppression therapy. **Avoid all live vaccinations e.g. Yellow fever, BCG, rubella, oral typhoid or polio.**
- **Avoid concomitant prescription of medications that interact with sirolimus (See BNF Appendix 1).**
- Communication with the Transplant Unit should the patient develop intercurrent illness.

Prednisolone

Indication	Immunosuppressive therapy to prevent rejection of solid organ allografts.
Formulations and strengths available	1mg, 5mg & 25mg tablets (plain) – soluble tablets available
Cost	https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff
Dose	Initial dose usually 20mg
Usual Dose Range	20mg, reducing to 5mg over 3-6 months, or withdrawn completely
Likely duration of treatment	Indefinite, as long as treatment is considered appropriate by specialist.
Contraindications	Known hypersensitivity to Prednisolone.
Warnings	Prolonged treatment with corticosteroids leads to adrenal suppression. Abrupt withdrawal of prednisolone in patients on long-term treatment can lead to a hypo-adrenal crisis, and precipitate an episode of acute rejection. **Avoid all live vaccines (e.g. yellow fever, BCG, rubella, oral typhoid (rarely prescribed), MMR and live (oral) polio - inactivated polio vaccine may be used).**
Side Effects (Full list in BNF)	Metabolic: hypertension, hyperlipidaemia, diabetes, weight gain Musculoskeletal: osteoporosis and avascular necrosis Increased risk of peptic ulceration Skin thinning and easy bruising Increased susceptibility to infection Increased risk of malignancy
Drug Interactions	Prednisolone and other corticosteroids are metabolised by multiple pathways, principally in the liver. Although drugs that either induce or inhibit these pathways will influence steroid metabolism, the prednisolone dose is not usually adjusted.
Monitoring	FBC, U&E, LFT, glucose, lipids and BP in Transplant Clinic (see page 4).

Contacts

1. Urgent advice and referrals

The on call Liver Unit Registrar (SpR) can be contacted via the hospital switchboard (0191 2336161)

2. Contact numbers

For further advice, contact the Liver Transplant teams on the following numbers:

Monday to Friday 08.00-17.00 hrs- Transplant Coordinators

Tel: 0191 2448068 / 0191 2231218	**Fax number:**	**0191 2231219**
All other times-	**Ward 7:**	**0191 2237007**

Consultant Hepatologists:

Dr Mark Hudson,
Dr Steven Masson,
Dr Stuart McPherson,
Dr Jessica Dyson,
Dr Mhairi Donnelly,
Dr Louise MacDougall

Consultant Surgeons:

Prof Derek Manas,
Prof Steve White,
Prof David Talbot,
Mr Jeremy French,
Mr Gourab Sen,
Mr Colin Wilson,
Mr John Hammond

Trust Name
NHS Trust

Private and Confidential

Shared Care Request/Confirmation

Consultant to complete first section of form and send to patient's GP.
GP to complete second section of form and return to hospital consultant within 28 days.

A copy of the full shared care guideline can be viewed at www.northoftyneapc.nhs.uk

Consultant .....

Department .....

Hospital .....

.....

Patient Details (use hospital label if preferred)

Name .....

Address .....

Postcode .....**Sex** .....

Hosp. Reg. No. .....**DOB** .....

Treatment Requested for Prescribing in Accordance with an Approved Shared Care Arrangement:

Diagnosis ....

Drug Name ..... **Dose**..... **Frequency** .....

Other Information (if appropriate)

Signed (Hosp. Dr)..... **Name (print)** ..... **Date**.....

To be completed by GP

Please tick one box

I ACCEPT the proposed shared care arrangement for this patient ☐
Or
I ACCEPT the proposed shared care arrangement with the caveats below ☐
Or
I DO NOT ACCEPT the proposed shared care arrangement for this patient ☐

My caveats / reason(s) for not accepting include:

Signed ..... **Name (print)** ..... **Date** .....
(Patients GP)

N.B. Participation in this shared care arrangement implies that prescribing responsibility is shared between the hospital consultant and the patient's GP