The Newcastle upon Tyne Hospitals NHS Foundation Trust

Institute of Transplantation, Freeman Hospital
Liver Transplant Unit Guideline

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1 Pre-operative Admission

When a suitable donor becomes available the transplant co-ordinator will be the first point of contact. The recipient will be contacted immediately, instructed to remain nil by mouth and make his/her way to the Liver Unit (the co-ordinator will arrange this).

On admission by the admitting doctor for elective transplantation:

1) ***Brief history and examination:*** The liver transplant clerking sheet should be completed http://nuth-vintranet1:8080/cms/Portals/0/HPB/periop/06_Liver Transplant_01_Clerking Form-May2012.doc

Exclude active infection or gross deterioration.
Ensure reason for transplantation and significant past medical history including each and every episode of complications from liver disease.

2) ***Bloods:*** FBC, Clotting profile, Crossmatch (10ml if already assessed)
Urea and electrolytes, LFTs
3 x 10mls clotted blood for microbiology
10 mls clotted blood for cytotoxic crossmatch

Total amount: 65mls blood

Group and antibody screen will have been done at assessment.
The transplant co-ordinator will request the blood transfusion requirements for theatre. This should include:

a) 18 units SAG-M buffy coat depleted red cells (and 12 units group specific to be held in reserve). More may be required in re-transplants, portal vein thrombosis, previous upper abdominal surgery
b) 30 units group specific FFP
c) 10 units platelets on site, 10 units platelets at BTS on standby.

Contact anaesthetist if:

Na <125 mmol/l or K <3.5 or >5.5 mmol/l
Mg <0.7 mmol/l or PO_4 <0.5 mmol/l
PT >20 sec
Fibrinogen <2
Hb <9 g/dl or Platelets <50 x 10°/l
Creatinine > 300
pH < 7.2 (where ABGs taken)

3) Other Specimens:

a) Nose, throat and perineal swabs (and additional swabs as necessary) will be taken by nursing staff
b) Arrange for MSU/CSU, sputum
c) Ascitic fluid if appropriate to exclude SBP.

4) ECG AND CXR if not performed within past 2 weeks.

5) Drugs/medication pre-op - prescribe the following:

a) Oral gut decontamination	Neomycin 1 g qds orally
	Colistin 100 mg qds or 1.5MU tds orally
	Nystatin 100,000 units qds mouth wash
	Nystatin 250,000 units qds per NG
b) Viral prophylaxis	Aciclovir 200 mg tds orally
c) Ulcer prophylaxis	Ranitidine 150 mg bd orally

6) Hepatitis B ± D: ***<u>For patients being transplanted for HBV and/or HDV</u>***
HB Ig 5000 units IV during anhepatic phase
(HB Ig is kept in pharmacy and must go to theatre with the patient)

7) Consent: Should have been obtained when patient placed on waiting list. Surgeon will reaffirm with patient immediately before transplant.

8) Research: If there is an ongoing research project contact the appropriate Research Registrar.

2 Peri-operative Management

2.1 Done by the Liver Transplant Anaesthetist

1. Antibiotics

INDICATION	**ANTIMICROBIAL PROPHYLAXIS**
LIVER TRANSPLANT	
First line	Piperacillin-tazobactam tds iv 4.5g for three doses
Penicillin allergy (no past medical history suggesting an anaphylactic reaction)	Meropenem 1g tds iv for 3 doses
Penicillin allergy (history suggestive of anaphylactic reaction to beta-lactams)	Teicoplanin* bd iv for 2 doses plus ciprofloxacin 400 mg bd iv for 2 doses plus metronidazole 500 mg tds iv for 3 doses
MRSA positive patients **Patients should also receive topical MRSA eradication, as per current Trust policy** http://nuth-vintranet1:8080/apps/policies/InfectionControl/MRSAPolicy201507.pdf	Add teicoplanin* bd iv for 2 doses if not already part of regimen
Complicated antibiotic history OR patient colonised / infected with multiresistant organisms OR previous history of *Clostridium difficile* associated diarrhoea	Contact microbiology for advice
RE-EXPLORATION EARLY POST-TRANSPLANTATION	Contact microbiology for advice; optimal prophylaxis will depend on timing post-transplant, current and previous antimicrobial history

***Teicoplanin dose is weight based**

<50kg: 600mg
50-80kg: 800mg
>80kg: 1g (1000mg)

2. Immunosuppression Methylprednisone 500mg iv just prior to reperfusion

3. Hepatitis B ± D **For patients being transplanted for HBV and or HDV**
HB Ig 5000 units IV during anhepatic phase

2.2 Done by Surgeon

1. Check Blood group match	Recorded on the Liver Transplant Operation Sheet
2. Check Donor details	Check the Electronic Offering System (EOS) and record in the Liver Transplant Operation Sheet
3. Paperwork at completion	Microbiology samples (e.g. ascites), histology form for explant/ Time 0 biopsy, Liver Transplant Operation Sheet, database entry

2.3 Done by Anaesthetist, Surgeon (with input from MDT/ Physician) at completion of surgery

1. Anticoagulation plan	Clearly recorded in Liver Transplant Operation Sheet (see Appendix)
2. Consider Basiliximab*	20mg iv given “on table” after haemostasis complete or within 6 hours of completion If Basiliximab is given, delay initial tacrolimus prescription (usually until day 5, or until transplant team decide to start) 2nd dose of Basiliximab to be given on day 4

Factors to be considered

Basiliximab should be considered in liver transplant recipients with:

- Chronic (NOT acute) renal impairment GFR<60
- Arterial conduit with supra-coeliac clamp
- Massive transfusion (where AKI is anticipated)
- Recipient of DCD liver
- Highly sensitised recipient (previous transplant/ known antibodies)

3 Post-Transplant Management

3.1 Drug check list

1. Nystatin 100,000 iu QDS mouthwash
2. Nystatin 250,000 iu QDS NJ/Oral
3. Neomycin 1 gm QDS NJ/Oral
4. Colistin 100 mg QDS NJ/Oral
5. Antibiotic prophylaxis (as per current guideline)
6. Aciclovir 200 mg TDS NJ/Oral
   Co-trimoxazole* 480mg po daily
   (*Dapsone 100mg od may be given as an alternative to co-trimoxazole in patients who have a history of rash with co-trimoxazole. However, it should be avoided in patients who have developed a more severe adverse drug reaction to co-trimoxazole. Contact Microbiology for advice if third line prophylaxis required)
7. If **acute** liver failure or **retransplantation**: usually also given antifungals – Contact Microbiology for advice
8. Ranitidine 50 mg IV - 8 hourly
9. Vitamin K 10 mg IV ODS for 72 hours

IMMUNOSUPPRESSION (to be prescribed by transplant team)

1. Tacrolimus (FK 506) 0.04 – 0.05 mg/kg twice daily
   NG/Oral x 12 hourly (will need adjustments according to levels – omit first dose if poor urine output or post-op creatinine > 1.5 x pre-op level). To be started within 48 hours.
   (accepted levels for FK506; 5 - 10 µg/l)
2. Azathioprine 1 mg/kg daily NG/Oral or IV
3. Hydrocortisone 100 mg IV x 12 hourly

ANTICOAGULATION

Anticoagulation regimen for all patients should be discussed with consultant anaesthetist and transplant surgeon. High-risk patients (PSC, PBC, HCC, Budd-Chiari) may need full anticoagulation. See appendix 6 for the current guideline about anticoagulation in liver transplantation.

Hepatitis B±D
HB Ig 5000 u IV daily for 5 days

3.2 Management in ITU

3.2.1 Day of Transplantation: Day 0

1. Investigations (on arrival in ITU)

Arterial blood gases, ECG & CXR
FBC, clotting, glucose, creatinine & electrolytes (including magnesium and calcium), LFTs as a baseline, lactate.

Repeat blood tests (except LFTs) within 2 hours, then at 4 - 6 hourly depending on the results.

Please Note the Following

A developing or worsening metabolic acidosis is a strong indicator of hepatic artery thrombosis (HAT). This is a potential disaster, which may be correctable surgically if diagnosed early (within an hour or two) but is otherwise likely to require urgent re-transplantation, which carries a 50% mortality. Other indicators of HAT include a rising PT and haemodynamic instability. Risk factors for HAT include: Hb > 10 g/dl, rapid platelet transfusion, aetiology of PBC, PSC or Budd Chiari.

If HAT is suspected, a Doppler Ultrasound must be obtained immediately; if this is equivocal, a hepatic arteriogram may be indicated. If HAT cannot easily be ruled out, urgent surgical re-exploration is usually required.

2. Ventilation: Normal ventilator settings (SIMV/BIPAP)
Limit PEEP to 5 cm H2O
Consideration of increasing PEEP > 5cmH_20 should be discussed with liver transplant anaesthetist
Maintain normocapnia unless acidosis demands hypocapnia (not less than PaCO2 3.5 kPa) to correct pH

Aim to wean as soon as following parameters numbers 1 - 3 are satisfied, and extubate when number 4 is satisfied:

1. PaO_2 > 12kPa, with FiO_2 <0.45
2. Haemodynamically stable
   - Not requiring large doses of inotropes / vasoconstrictors
   - Not bleeding excessively (eg <100 ml/hr)
   - Not requiring continual fluid filling (< 500 ml/hr)
3. Core temperature > 36.0 °C
4. $PaCO_2$ < 7.0 kPa when breathing spontaneously

3. Fluid balance:

Refer to post-operative instruction form with directive actions from the Consultant Anaesthetist.

Bleeding	If drain loss >150 ml/hr for 3 hours repeat FBC, PT and do Cardiac output and CALL CONSULTANT ANAESTHETIST.
Fluids	Crystalloid: As per tight insulin regime (10% dextrose 84ml/hr). Give colloid to maintain CO / urine output / filling pressures etc. If Hb < 8.5 g/dl, give blood (aim for Hb 8.5 - 10 g/dl) If PT > 25 s, (or other value set by the anaesthetist), give FFP Otherwise use gelatins or Albumin Platelets should not be given unless platelet count < 20, or patient actively bleeding. Any platelet transfusion should be discussed first with transplant anaesthetist Any platelets that are given should be given slowly; over at least 1 hour Cryoprecipitate as instructed using lab results.

4. Drugs

Analgesia	Fentanyl (50-200 mcg/hr), alfentanil (2-4mg/hr) Remifentanyl (0.1-0.3mcg/kg/hr) Morphine PCA (standard) after extubation.
Sedation	Propofol 5-20 ml/hr Midazolam 1 - 4 mg IV bolus prn as an additional sedation if required.
Inotropes	As prescribed by transplant anaesthetist. See Handover sheet.
NAC	May be prescribed postoperatively to support poor initial liver function
Electrolytes	Mg if > 80 mmol KCl required/day or level <0.70 mmol/l Calcium 10% $CaCl_2$ may be required if patient requiring further FFP, or if ionised calcium less than 0.8.
Insulin	Post liver transplant patients frequently become hyperglycaemic, and this is often resistant to treatment. It is usually short lived.

Insulin may be given according to the ITU tight-insulin regimen.

Anticoagulation

Should be confirmed with consultant surgeon / transplant anaesthetist. (Full anticoagulation may be required for some patients. Only after discussion with consultant surgeon/anaesthetist.)

Antibiotics }
Oral gut decontamination }
Viral prophylaxis } **See drug check list**
Pneumocystis pneumonia prophylaxis }
Peptic ulcer prophylaxis }
Immunosuppression }
Vitamin K }
Hep B ±D prophylaxis (if necessary) }

Others Check that patient was not taking other long-term medications

3.2.2 Day 1-3

1) Investigations Bloods to be done daily: FBC, Coagulation screen
Na, K, RBG, ionised calcium, Mg, LFTs, lactate, PO_4,
Tacrolimus trough
Ensure donor and recipient CMV status is known and documented

2) Ventilation Weaning discuss with the anaesthetist: see parameters on day 0

3) Fluid Balance As for day 0

4) Drugs Add Colistin nebulisers 0.5-1 Megaunits bd if patient not extubated at 48 hours

5) Nutrition Commence NJ feeding (Osmolite 25 mls/hr initially, Nepro if renal failure)
Confirm with transplant team feeding regimen

6) Additional Procedures

- Day 1 post op - Liver Team to arrange Doppler Ultrasound

<u>General points for patients continuing on ITU:</u>

Most aspects of management are in accordance with good routine ITU practice.

Bloods Daily: FBC, coagulation screen, U&E, LFTs, Ca++, Mg++, phosphate, lactate.
Tacrolimus trough level checked in the morning

Maintain Hb at 8.5 to 10g/dl (risk of hepatic artery thrombosis if >10) may require venesection – discuss with anaesthetist/surgeon

Drugs Oral gut decontamination continues until patient is on a normal diet
If tolerating feed, switch hydrocortisone to prednisolone 20 mg/day and
IV drugs to oral
Immunosuppression varies in accordance with ward rounds and trough levels

Feeding Aim to start enteral feeding on day 1 but liaise with surgeons first

Lines/Drains Lines should be changed or removed as per ITU practice
Removal of drains after discussion with surgeons.

3.3 Return to Main Ward

There must be a proper <u>ITU doctor to Ward 38 or 12 doctor handover</u>

Main concerns now are <u>sepsis</u> and <u>rejection</u>

If day 1 to 3, follow ITU protocol otherwise check the following:

Specimens: FBC: aim for an Hb of 8.5 - 10 g/dl
PT: a rising PT is a sign of sepsis, rejection or hepatic artery thrombosis
Electrolytes (for renal function), Mg/Ca/PO_4 *daily*

Fluid balance: Drain loss
Urine output – if poor look at CVP, and conduct a fluid challenge. If filled (i.e. CVP rises and stays elevated after 250 - 500 ml of colloid) and urine output <30 mls/hr discuss with SpR - may consider inotropes
Remember that oliguria is usually due to hypovolaemia. Frusemide is for fluid overload not oliguria.

Respiratory Function:
Pulse oximetry and ABG to assess
If desaturates think of pleural effusion, infection, pulmonary oedema, mucus plugs, exhaustion
May need CXR / physio / supplemental 02 / antibiotics / US and then drainage
Avoid draining pleural effusions unless agreed with the ITU Consultant and Consultant Surgeon.

Discuss with SpR and then consultant anaesthetist if needs ventilation

Drugs (see checklist)

Immunosuppression
Tacrolimus dose varied according to morning level.
Prescribed by transplant team. Early post-op trough levels should be between 5-10µg/l
Azathioprine 1mg/kg daily
Prednisolone 20 mg daily (if not absorbing use hydrocortisone 100mg bd)

Nutrition Oral/NJ feeding

If suspect sepsis **? Source (lines / chest / urine / wound)**
Culture urine / sputum / wound / blood
Discuss with microbiologist re appropriate antibiotics
Consider intra-abdominal sepsis and investigate appropriately

If suspect rejection Liver biopsy (need US of liver/biliary tree before biopsy)
liver team to contact histopathologist prior to biopsy for urgent report
Check PT and platelets – Discuss with Senior if results abnormal

If suspect Hepatic artery occlusion
Urgent Doppler of vessels and consider angiogram
Contact transplant team immediately

3.4 Discharge

An INTIME discharge summary to be completed by SHO/Registrar on the day of discharge to GP

GP needs to know: Reason for transplant
Complications
Ongoing problems
Drugs - General
Immunosuppression
Follow up arrangements

Liver transplant clinic
Liver transplant recipients will be followed up in the dedicated liver transplant clinic on Thursday 1315-1400 for the first 6 months

After 6 months, follow-up returns to the Transplant Hepatologist clinic

Appendix 1

Acute Liver Failure

Please see separate Guidelines for the Management of ALF

Microbiological Aspects of Care

LIVER UNIT ANTIMICROBIAL GUIDELINES

Current Liver Unit Antimicrobial Guidelines are available on the trust intranet:

INFECTION PREVENTION AND CONTROL

All Trust Infection Prevention and Control policies must be strictly adhered to. These are available on the Trust intranet.
Please pay particular attention to Trust policies on Hand Hygiene, Standard precautions and Isolation.

General considerations for ALL liver transplant patients:

1. Patients must not be present while baths are run or drained
2. Visitors should be free of potentially transmissible infections
3. Visits from pre-school aged children should be actively discouraged, especially in the early post-operative period
4. A high standard of food hygiene must be followed. Certain foods must be avoided including fresh fruit, vegetables or salads (unless they have been thoroughly washed); soft cheeses and pâtes; undercooked meats; raw eggs and dried spices and pepper.

Additional precautions during the immediate post-operative period, during episodes of augmented immunosuppression or when patient's white cell count is $<2x10^6$/L:

1. Patient should be nursed in a single cubicle with an airlock whenever possible. Where switchable ventilation is provided this is preferable and it must be set for POSITIVE pressure ventilation in accordance with Trust isolation policy
2. Members of staff entering the cubicle should be kept to the minimum number possible
3. Patient's visitors should be restricted to the same two nominated close relatives or friends and pre-school aged children must not be allowed to visit
4. It is essential that staff and visitors entering the patient's cubicle are not suffering from any potentially transmissible viral or bacterial infection
5. Visitors entering the patient's cubicle will need guidance relating to appropriate precautions including hand hygiene and the use of personal protective equipment, in line with Trust policy
6. Drinking water must be sterile, canned or boiled.

Additional precautions for transplant recipients known or suspected of being infected/colonised with potentially transmissible micro-organisms:

1. Patients must be nursed in standard isolation in a single cubicle, preferably with an airlock. NEGATIVE pressure ventilation facilities must be used whenever possible, in accordance with Trust isolation policy
2. Appropriate infection prevention and control precautions must be instituted in line with Trust policies.

FURTHER MICROBIOLOGICAL CONSIDERATIONS

1. All patients to receive the following prophylaxis as soon as they can tolerate oral medication:

Aciclovir 200 mg orally, eight hourly
Cotrimoxazole 480 mg orally once daily

These are to be continued until the Prednisolone dosage is reduced to 5 mg or lower and re-instituted with augmented immunosuppression.

2. Any patient ventilated for longer than 48 hours should be given nebulised Colistin 0.5-1MU bd whilst intubated

3. On Discharge**:** Patients should be issued with the Liver Transplantation handbook containing advice for the avoidance of infections and educated whilst on the ward. Patients should report any pyrexia to GP or Transplant Centre. Patients must notify Transplant Centre if they come in to contact with anyone known to be suffering from communicable infections including the following:

Chicken Pox, Tuberculosis, Measles, Hepatitis

4. GPs should be dissuaded from prescribing any anti-microbial chemotherapy without consulting the Transplant Centre. Wherever possible, appropriate specimens should be collected before empirical antimicrobial therapy is commenced.

Appendix 3

Vaccinations in adult liver transplant recipients
(Dr Sheila Waugh, Dr Kathy Walton, Dr S Masson)

Recommended
Consider
Contraindicated

Pre-transplant

Vaccination response is often diminished in patients with organ failure and patients who are immunosuppressed, thus vaccination should be considered early in the course of disease. Most vaccines recommended for patients who may require liver transplant are also recommended for those with chronic liver conditions.

Live vaccines should not be given to patients who may be transplanted (and hence become immunosuppressed) within 4 weeks of the last vaccine dose. Live vaccines include the shingles vaccine, varicella vaccine, MMR, BCG, yellow fever and some typhoid vaccines.

If possible, inactive vaccines should be given at least 2 weeks prior to immunosuppression/transplant, otherwise it may be preferable to wait until after transplant when response is likely to be better.

Vaccine	Vaccine type	Comment
Influenza	Inactive	Recommended annually
Hepatitis B	Inactive	0, 1, 2 and 12 month intervals Response can be checked by testing Anti-HBs levels 2-4 months after the last dose. Consider a further 3 dose course if <10 IU/L. Consider a single booster dose if 10-100 IU/L
Hepatitis A	Inactive	One dose with a booster 6-12 months later
Pneumococcal PPV23	Inactive	One dose
Human Papilloma Virus (1)	Inactive	Consider in young adults who have not previously been vaccinated
Tetanus/diphtheria/pertussis	Inactive	Ensure up to date with current UK schedule
Polio	Inactive	Ensure up to date with current UK schedule
Meningococcal	Inactive	Ensure up to date with current UK schedule

(1) Human papilloma virus vaccine is routinely recommended in the UK for girls at age 12-13 years. It would not normally be recommended after age 18. The current UK vaccine (Gardasil) provides protection against HPV 6, 11, 16 and 18.

Post-transplant

Live vaccines are contraindicated

Inactive vaccines are not contraindicated in the immunosuppressed, however, they may elicit lower levels of protection than in the immunocompetent. For this reason it is best to delay vaccination (other than seasonal influenza vaccination) until baseline levels of immunosuppression are reached (e.g. 3 months after transplant).

The following vaccines should be given to liver transplant recipients:

Vaccine	Vaccine type	Comment
Influenza	Inactive	Should be given annually (wait 4 weeks post-transplant.) The live intranasal vaccine should not be given
Hepatitis B	Inactive	If not given pre-transplant (see above). Also consider a further dose of these vaccines if they were given within the two weeks immediately prior to transplant
Hepatitis A	Inactive	If not given pre-transplant (see above). Also consider a further dose of these vaccines if they were given within the two weeks immediately prior to transplant
Pneumococcal PPV23	Inactive	If not given pre-transplant (see above) Also consider a further dose of these vaccines if they were given within the two weeks immediately prior to transplant
Human Papilloma Virus (1)	Inactive	Consider in young adults who have not previously been vaccinated
Tetanus/diphtheria/pertussis	Inactive	Ensure up to date with current UK schedule
Polio	Inactive	Ensure up to date with current UK schedule
Meningococcal	Inactive	Ensure up to date with current UK schedule

Live vaccines should not be given post-transplant:

Zoster vaccine	**Contraindicated. Live vaccine. NB Patients may receive a routine call for this vaccine at 70 years. It is important that patients and GPs are aware that this is contraindicated in immunosuppressed patients. If inadvertent zoster vaccination occurs seek specialist advice on further management**
Varicella	**Contraindicated. Live vaccine**
MMR	**Contraindicated. Live vaccine**
BCG	**Contraindicated. Live vaccine**
Yellow Fever	**Contraindicated. Live vaccine (If travelling to an endemic area, seek expert advice)**
Smallpox	**Contraindicated. Live vaccine**
Live typhoid vaccine	**Contraindicated. Live vaccine**

Travel-related vaccination: Transplant patients planning travel abroad should receive all inactive vaccines and malaria prophylaxis recommended for the area in which they intend to travel. Where live vaccines would normally be recommended, seek expert advice as these are contraindicated post transplantation.

Vaccination of household contacts

As transplant patients may receive less protection from vaccines and cannot receive live vaccines, vaccination of household contacts can provide significant protection by reducing exposure.

All household contacts and in particular children, should receive vaccinations as per the routine UK schedule. The risks posed by use of live vaccines in contacts of transplant recipients are far less than the risks wild type infection would pose.

Additional points to note:

Vaccine	Vaccine type	Comment
Influenza	Inactivated	This is recommended annually under UK guidelines for the household contacts of immunosuppressed individuals
Influenza	**Live attenuated (part of routine UK childhood vaccination) (2)**	**Live intranasal vaccine is not recommended for household contacts of transplant recipients as live virus can be shed following vaccination, and thus poses a theoretical risk. Children who would otherwise qualify for the live vaccine should ideally receive the inactivated injected vaccine instead**
Varicella	Live	This is recommended for any household contacts who do not have a history of chickenpox. It can be safely administered to household contacts of the immunosuppressed. 5-10% of vaccine recipients develop a localised rash in the 4 weeks following vaccination – if this occurs contact with the transplant recipient should be avoided
MMR	Live	Give as per UK schedule. This can be safely administered to household contacts of the immunosuppressed
Rotavirus	Live oral	Give as per UK schedule. This vaccine is given to infants at 2 and 3 months of age, and is a live attenuated oral vaccine. Vaccine strain virus will be excreted in stool for approximately 2 weeks, and during this time strict personal hygiene is required, in particular hand hygiene after nappy changes

(2) In 2016, the live intranasal influenza vaccine was offered to all children aged 2, 3 and 4 years and in school years 1, 2 and 3 (and older in some pilot areas). Over the coming years vaccination is intended to extend to all children aged 2-17 years. The live intranasal vaccine is also the vaccine normally recommended for children with risk factors for influenza (other than immunosuppression).

References

Immunisation against infectious Disease. (The Green Book). Public Health England. https://www.gov.uk/government/collections/immunisation-against-infectious-disease-the-green-book (accessed October 2016)

Vaccination in Solid Organ Transplantation. L. Danziger-Isakov et al. Am J Transplant. 2013; 13: 311-317

2013 IDSA Clinical practice guideline for vaccination of the immunocompromised host. Rubin et al. CID 2014; 58: e44-e100

Appendix 4

CMV

1. Pre-transplantation – Ensure that a plain clotted blood sample is sent to Microbiology for CMV IgG testing. NB – this result may be erroneous if the blood is collected after blood transfusion or administration of other blood products
2. At time of transplant – Ensure donor and recipient bloods are sent for CMV IgG testing. When results are available, document them clearly in the notes.

CMV prophylaxis

- Given to CMV mismatches – (i.e. donor CMV IgG positive, recipient CMV IgG negative) and CMV positive recipients with steroid-resistant rejection
- Give prophylactic oral valganciclovir (900 mg od po) for 90 days starting at day 10 post liver transplant
- In presence of renal impairment, reduce dose according to creatinine clearance (see attached sheet for calculation)
- If oral valganciclovir cannot be given, consider the use of iv ganciclovir
- If these agents are contraindicated, consider CMV monitoring and pre-emptive treatment. This entails testing CMV PCR every week for three months starting two weeks post transplantation. Pre-emptive therapy with oral valganciclovir (900mg bd po for two weeks, or a renally-adjusted dose in the presence of renal impairment) is indicated if the viral load is ≥1 x 10^4 copies/mL. Treatment may be considered at lower levels if the patient has potentially CMV-related symptoms
- Consideration may also be given to the use of CMV high titre IVIG, together with CMV monitoring and pre-emptive treatment as above
- Please ensure that prophylaxis is stopped after the 90 day course has been completed.

CMV Disease

Patients with CMV disease may be present with a combination of symptoms and signs. These include the following: unexplained fever, malaise, leukopenia, pancytopenia, deterioration in liver function, pneumonia, gastrointestinal disorder e.g. nausea, diarrhoea, abdominal pain. It will be relatively uncommon for patients receiving prophylactic valganciclovir to develop CMV disease, but the diagnosis must not be discounted in this group and the index of suspicion should be raised in the context of recently augmented immunosuppression or non-adherence.

It is important to remember that liver transplant recipients may have other reasons for developing these symptoms and signs and consideration should be given to additional investigations as appropriate. These may include reviewing medication, performing a liver biopsy, bronchoalveolar lavage, endoscopy with biopsy etc.

Investigations for CMV disease *include:*

a) **CMV PCR**. Send EDTA blood to microbiology by arrangement with a Freeman Microbiologist. For same day results, the specimen must be received in the microbiology laboratory before 8.45 am.

b) **Histological evidence of CMV disease** - If appropriate send relevant biopsy, e.g. hepatitis, gastritis, colitis, pneumonitis.

If the diagnosis of CMV disease is not clear cut and the patient is not acutely unwell it may be helpful to repeat the CMV PCR test after an interval of a few days in order to monitor the trend in viral load.

Treatment of CMV disease

- If CMV disease has been diagnosed please consider treatment *after discussion with consultant microbiologist and transplant team*. Viral loads of ≥10^4 copies/mL are usually considered diagnostic in symptomatic patients, although treatment may be indicated at lower levels in certain circumstances
- If the patient is not severely unwell and if they are able to tolerate oral medication, consider treatment with oral valganciclovir 900mg bd (reduce dose in renal impairment according to creatinine clearance – see table). Treatment should normally be for at least 2 weeks and until there have been two consecutive negative CMV PCR results. For asymptomatic patients with stable low level CMV viraemia, it may be appropriate to consider stopping treatment without obtaining a negative CMV PCR, however, this should be discussed on a case by case basis
- Minimise immunosuppression
- For severely ill patients, or those who cannot tolerate oral medication, give iv ganciclovir with reduction of immunosuppression. The usual dose is 10 mg/kg per day in 2 divided doses for 10-21 days as above, depending on the severity of disease and clinical response. The dose should be adjusted in renal impairment
- During treatment monitor full blood count, renal function, liver function and clinical response regularly. Further CMV PCR may be indicated. Please discuss this with a Consultant Microbiologist
- If valganciclovir or ganciclovir are contraindicated, or ganciclovir resistance is suspected, consider the use of foscarnet (currently unlicensed for this indication). The recommended dose in patients with normal renal function is 60mg/kg every 8 hrs, given by infusion over at least one hour. The dose should be reduced according to the data sheet in patients with renal impairment.

Special warnings and precautions for use:

Valganciclovir and ganciclovir

- Prior to treatment with either agent, patients should be counselled that these drugs may be potentially carcinogenic. Patients of child bearing age should be counselled about the risks of teratogenesis, mutagenesis and infertility
- IV ganciclovir should ideally be given via a central line
- Myelosuppression is a major side effect. GCSF may be indicated in some cases of neutropenia associated with these drugs (absolute neutrophil count < $1 \times 10^{\wedge}9$/L).

Foscarnet

- Administration of foscarnet may lead to renal impairment and electrolyte imbalance including hypocalcemia, hypomagnesemia and hypokalaemia. Urea and electrolytes should therefore be checked regularly. The risk of renal toxicity may be reduced by ensuring adequate hydration of the patient prior to the administration of foscarnet.

Valganciclovir dosage for patients with renal impairment

Approximate creatinine clearance may be calculated as follows:-

Male Creatinine Clearance (ml/min) = [140 – Age] x Weight* (kg) / 0.81 x Creatinine (micromol/L)

Female Creatinine Clearance (ml/min) = 0.85 x male value

***Use ideal body weight calculated by the formula given below:

Ideal male body weight (kg) = 0.9 x [Height (cm) – 154] + 50
Ideal female body weight (kg) = 0.9 x [Height (cm) – 154] + 45.5

Creatinine Clearance (ml/min)	Valganciclovir prophylaxis	**Valganciclovir treatment dose**
≥60	900mg OD	900mg BD
40-59	450mg OD	450mg BD
25-39	450mg every 2 days	450mg OD
10-24	450mg twice weekly	450mg every 2 days
<10**	IV **GANCICLOVIR (not valganciclovir)** 1.25mg/kg OD (post dialysis on dialysis days)	IV **GANCICLOVIR (not valganciclovir)** 1.25mg/kg OD (post dialysis on dialysis days)

** Valganciclovir is not recommended for patients on dialysis, therefore patients with a creatinine clearance <10ml/min or who are on dialysis or CVVH should be discussed with the transplant microbiologist

Note:

- ➔ Valganciclovir treatment for prophylaxis of CMV can be started up to 10 days post-transplant
- ➔ The main side effect of valganciclovir and ganciclovir is myelosuppression
- ➔ The above formulae only give an estimate of creatinine clearance, therefore careful attention should be paid to white cell count and clinical response
- ➔ Alternatively, formal creatinine clearance testing may be performed.

Appendix 5

Hepatitis B (HBV) & Hepatitis C (HCV)

Hepatitis B

During transplant assessment

Ensure the following serology is available:

HBsAg
HBeAg & Ab
HBV DNA level [viral load]
Anti-viral resistance testing
Delta Ab
HCV Ab
HIV Ab

All patients with HBV cirrhosis should be on long-term viral suppressive therapy to suppress the HBV DNA levels to undetectable levels. The preferred treatment is tenofovir or entecavir as these have very low risk of anti-viral resistance and the majority will achieve undetectable HBV DNA levels (<20IU/ML). Occasionally patients may require the addition of a second antiviral to achieve undetectable HBV DNA levels.

Patients who present acutely with elevated HBV DNA levels (acute HBV or flare of chronic HBV or liver failure due to another cause on a background of HBV) who are not on antiviral treatment should have this commenced prior to liver transplantation or early post-liver transplantation.

At time of transplant

The aim is to prevent HBV recurrence with use of both anti-HBs (HBIg) and antiviral agents (tenofovir or entecavir)

HB Ig: Polyvalent hepatitis B Immunoglobulin

HBIg is given to prevent recurrent hepatitis B

HBIg should be given;

i) In theatre during anhepatic phase (obtain from pharmacy and send to theatre with patient)
ii) Daily for 5 days post-transplant
iii) All patients should have an HBV DNA taken around the time of transplant

- Patients who have HBV DNA levels <20IU/ML on treatment with tenofovir or entecavir do not require further HBIG after 5 days
- Patient with elevated HBV DNA levels need to continue HBIG with the aim of maintaining anti-HBs level > 100 IU

o Check weekly initially, subsequently fortnightly and then monthly
o Check more frequently if there has been significant blood loss
o Normal requirements are 4-8 weekly in first year and thereafter 6 – 12 weekly
o Dose: 5000 Units IV (diluted in pharmacy), give over 30 minutes (Side effects: Rare - arthralgia, anaphylaxis, immune complex disease)

- When HBV DNA levels become undetectable on antiviral treatment HBIG can stopped.

Antiviral Medication

- Continue tenofovir or entecavir post-op indefinitely, aiming to keep the HBV DNA undetectable and ideally HBsAg negative
- For patients with renal impairment (eGFR <60) entecavir is the preferred antiviral drug as it has less propensity to cause renal dysfunction
- Both drugs require dose reduction in renal impairment.

Past HBV infection or HbcAb positive liver

For patients with a past history of HBV infection (HBcAb pos, but HBV DNA undetectable) or those who receive a HBcAb positive liver, treatment with lamivudine (least expensive), entecavir or tenofovir should be started to prevent reactivation of HBV immediately post liver transplantation.

Immunosuppression

Our standard immunosuppression should be used. However, where possible the steroid dose should be kept as low as possible, as HBV DNA contains a steroid responsive element and steroids increase viral replication in recurrent disease.

Hepatitis C

HCV reinfects the graft rapidly after liver transplantation in patients who are viraemic at the time of transplantation. Refer to the **viral hepatitis team guidelines** for the management of recurrent HCV.

Appendix 6

Immunosuppression

1. *Indications to withdraw azathioprine temporarily – restart when no longer relevant:*

   WBC < 3.0
   Active CMV infection
   Hepatotoxicity
   Clinically important sepsis

2. *Indications to withdraw azathioprine*

   Viral Hepatitis

3. *Threshold for dose reduction of azathioprine:*

   WBC < 4.0

4. *Mycophenolate mofetil (MMF) to be considered in the future*

5. *When prednisolone is reduced to a daily dose of 5 mg or less then prophylactic ranitidine, nystatin, septrin (or dapsone) and aciclovir can be stopped*

6. *Consider maintaining patients with autoimmune hepatitis on long-term low dose steroids (prednisolone 5 mg/day) due to possible disease recurrence.*

Appendix 7

Thymoglobulin

Thymoglobulin (Rabbit ATG)

Thymoglobulin (rabbit anti-thymocyte globulin or rATG) is a polyclonal antibody produced in rabbits immunized with T lymphocytes derived from human thymus tissue. The purified product contains antibodies specific for:

- T lymphocyte cell surface molecules including CD3, CD4 and CD8
- Adhesion molecules
- Cytokine receptors, including the IL2 receptor subunit (CD25)
- Cell surface antigens also expressed by some B lymphocytes, plasma cells and monocytes

Consequently, administration of Thymoglobulin has multiple effects on both the adaptive immune response (including T lymphocyte activation [leading to cytokine release], clearance of T lymphocytes from the circulation), and innate pro-inflammatory responses (inhibition of cell adhesion and leukocyte/monocyte migration into tissues).

Indications
In liver transplant recipients, thymoglobulin is used in the treatment of steroid resistant rejection and/or the treatment of antibody-mediated rejection. However, the decision to use ATG will always involve senior members of the liver transplant team.

The protocol for the usage of ATG protocol is outlined in detail in Appendix G of the Freeman Hospital Renal Transplant Protocol:

Appendix 8

Anticoagulation

The current Liver Transplant Anticoagulation Guideline is available on the Trust intranet