

**PROTOCOL FOR
IN-PATIENT MANAGEMENT
FOLLOWING
LIVER TRANSPLANTATION**

Updated by Dr Andrew Bathgate
Scottish Liver Transplant Unit
Royal Infirmary
Edinburgh
Updated March 2019

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APPENDICIES

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This protocol describes the management of patients immediately pre-transplant and following liver transplant during their hospital stay.

ADMISSION FOR TRANSPLANTATION

When a liver becomes available from the National Allocation Offering System, the transplant co-ordinator and consultant surgeon will be informed. If it is not a named patient offer they will identify a suitable recipient from the waiting list. The medical registrar will be informed. The transplant co-ordinator will contact the potential recipient and consultant hepatologist.

On admission the following will be carried out:

1. Admission history and examination concentrating particularly on events since the patient's most recent review.
2. Investigations:
 - Full blood count
 - Liver function tests including GGT, AST + TP
 - Full coagulation screen
 - Urea, creatinine, sodium, potassium and total C02.
 - Glucose
 - Electrocardiogram
 - Abdominal ultrasound if not done in previous 4 months
 - CT scan IF re-do liver transplant > 3 months from last scan to assess portal vein patency
3. Consent for operations signed by patient (*or reaffirmed*).
4. Blood transfusion - **Cross match 10 units of red blood cell concentrate**
5. The patient may have given consent to a clinical trial. Information regarding the trial will be at the front of the notes and will highlight any additional bloods or procedures required. The research nurse or Investigator should be made aware the patient has been admitted for transplant. They can also be contacted if there are any concerns regarding the trial.

MANAGEMENT POST LIVER TRANSPLANT

Intensive patient monitoring is required in the early postoperative period. Initial emphasis is on ventilation and cardiovascular stability, and thereafter on fluid balance, urine output and early graft function. Screening for infection and graft dysfunction becomes important later.

Patient management following transfer from theatre to the Intensive Care Unit will be considered under the following headings:

1. Cardiovascular system
2. Ventilation
3. Fluid & electrolyte balance/Biochemistry
4. Renal Function
5. Coagulation
6. Microbiology and antibiotics
7. Immunosuppression
8. Pain relief and anxiety
9. Nutrition
10. Liver function

TRANSFER FROM THEATRE TO INTENSIVE CARE UNIT

- 1 Immediately before transfer from theatre haemodynamic and biochemical parameters will be checked and corrected appropriately.
- 2 During transfer ECG, SaO₂, arterial pressure, and where indicated pulmonary artery pressure and intracranial pressure will be continuously monitored.
- 3 On arrival in ITU at least one monitored cardiovascular parameter should be displayed continuously during transfer to ITU monitoring.
- 4 In stable patients, the pulmonary artery pressure catheter will be removed in theatre or immediately after arrival in ITU.
- 5 Paralysis should be maintained until the patient is fully monitored and established in ITU.
- 6 The anaesthetist supervising the transfer will report on the patient's condition to the medical ITU staff on-call.
- 7 Hydrocortisone will be written up and administered peri-transplant. The immunosuppressive regimen will be finalised and written up on first post-operative transplant ward round.

1. CARDIOVASCULAR SYSTEM

1.1 Principles

Correction of intravascular volume is the first line of therapy. If patient is cold, they will need increased intravenous fluids over baseline requirements as rewarming occurs.

Hypotension may be caused by hypovolaemia secondary to bleeding or to inadequate fluid replacement, by cardiac dysfunction consequent on arrhythmia or myocardial depression, or by vasodilatation due to graft dysfunction or sepsis (*Appendix 1*).

1.2 Aims

- Stability.
- Rapid detection of problems e.g. haemorrhage.
- Earliest removal of invasive monitoring lines.

1.3 Monitoring

The following measurements should be recorded for at least 24 hours post-op, thereafter as clinically indicated.

<u>Measurements</u>	<u>Frequency of recording</u>
Heart rate	Continuous
ECG - 5 lead for ST analysis	Continuous
CVP	Continuous
Arterial blood pressure	Continuous
SvO ₂	Continuous
PAP *	Continuous
PCWP *	Ad hoc/after interventions and as indicated.
Cardiac output *	Continuous
SVR *	After interventions, and as indicated
Core temperature	Continuous
Peripheral temperature	Continuous

* If Swan-Ganz catheter in place

2. **VENTILATION**

2.1 **Chest X-ray**

A chest x-ray should be performed on admission to ITU.

2.2 **Ventilator settings**

Airway pressures, tidal and minute volumes should be recorded hourly. Aim for peak pressure < 40 cm H₂O. Values used intraoperatively will be a good guide to appropriate minute volume and required inspired oxygen concentration.

As a guide:

Tidal volume	500 ml,
Resp rate	12
Inspired O ₂	0.5 initially

Arterial blood gases should be measured on admission and where indicated thereafter. The minimum inspired oxygen to achieve SaO₂ > 95% with PaCO₂ approximately 4.5 kPa should be employed.

2.3 **Spontaneous Respiration**

Aim for early spontaneous respiration as soon as possible (normally 12-24 hours). Adequate analgesia aids effective spontaneous respiration. Physiotherapy, using intermittent positive pressure from the Bennett, may help to prevent basal atelectasis after extubation.

2.4 **Extubation**

The criteria for extubation are as follows: -

Short trial on C-circuit or SV via Drager ventilator before endotracheal tube removal.

Patient should be/have:

1. Conscious (does not require cessation of analgesia).
2. Able to protect airway.
3. On minute ventilation < 10 l/min, F_iO₂ 0.4 or less.
4. Full return of neuromuscular function.
5. No gross problems with chest secretions and an acceptable chest xray.
6. Stable haemodynamics and renal function.
7. No immediate likelihood of return to theatre.

3. FLUID AND ELECTROLYTE BALANCE/BIOCHEMISTRY

- 3.1 If graft is functioning, expect correction of acidosis, fall in blood lactate and fall in serum potassium requiring K⁺ replacement. Glucose will usually be normal or high, falling spontaneously to normal. Low glucose requiring replacement indicates poor graft function.

The aim is to maintain normal body mass and extracellular fluid composition by means of weighing, serum electrolyte measurements and calculation of fluid and solute balances. This is especially important in the case of sodium. The electrolyte content of drugs must be considered.

- 3.2 Urine output should be measured hourly. Volumes of fluid from abdominal drains and nasogastric tubes should also be recorded. Accurate fluid balance recording is important. Weight should be recorded daily once the patient is mobile.

- 3.3 The laboratory measurements required in the first 24 hours are listed in *appendix 2*. Thereafter urea and electrolytes, liver function tests, full blood count and prothrombin time should be measured **daily for the first 7 days**, then **three times weekly till discharge**. Calcium, phosphate and magnesium should be measured at least weekly. **Avoid unnecessary blood sampling.**

3.4 Potassium:

Ciclosporin and tacrolimus can cause electrolyte imbalance, including hyperkalaemia and hypomagnesaemia, with or without renal impairment.

Hypokalaemia: Potassium chloride solution, diluted to 40 mmol/100 ml saline may be infused over 2 hours to correct hypokalaemia.

Hyperkalaemia: if serum K > 6.0 mmol/l.

- i) Acute /early post op, iv fluid stage:
 - a) Correct with dextrose/insulin
 - b) Assess renal function
 - c) Consider reduction in Ciclosporin/Tacrolimus dose
- ii) Chronic/late post op stage:
 - a) Check blood Ciclosporin/Tacrolimus concentration, and reduce dose by 20% if levels are above therapeutic range.

- b) Commence low potassium diet (SLTU dietician bleep 2907)
- c) Treat with calcium resonium 15 g tid.

3.5 Magnesium

Serum magnesium should be measured at least weekly. In addition it should be measured urgently if necessary if the patient develops a) cardiac dysrhythmia or b) neurological dysfunction. The regimen used to correct hypomagnesaemia in critical care is 20mmol Magnesium in 100ml glucose 5% administered over 4 hours (see critical care monograph for Magnesium)

<http://intranet.lothian.scot.nhs.uk/Directory/CriticalCare/Critical%20Care%20Guidelines/Drugs%20and%20fluids/MAGNESIUM%20updated%202017.pdf>

3.6 Glucose

Bedside measurements for glucose are adequate unless gross abnormality is present. Maintain blood glucose at 8 or less using standard glucose control regime.

4. **RENAL FUNCTION**

Plasma urea and creatinine should be measured daily.

Oliguria

Appendix 3 is a flow chart for the management of oliguria (urine output < 40ml/hr).

Oliguria should be treated in relation to the CVP (or PCWP if available). Intravenous fluid therapy should be increased if the CVP or PCWP is low and continued until it returns to normal. If uncertain whether hypovolaemic, observe CVP (or PCWP), HR, BP and urine output response to 200 ml Plasmalyte over 15 mins. If no response or oliguria occurs without hypovolaemia, consider graft dysfunction, sepsis and nephrotoxic drugs (*Appendix 4*). Furosemide may be useful eg. 20 mg IV bolus.

Established renal failure will require continuous veno-venous haemofiltration (CVVH) via a central venous double lumen catheter (eg. Quinton line). Contact the renal registrar (bleep 5285 (day) #6394 (out of hours)). Filter patency is usually maintained using heparin or prostacyclin. Avoid heparin if severe coagulopathy, avoid prostacyclin if hypotensive.

5. **COAGULATION/TRANSFUSION**

5.1 Measurement of coagulation

Coagulation screen will be performed 0, 6, 12 and 24 h post-operatively. Thereafter prothrombin time will be measured daily for 7 days, then as indicated. After the first post-operative day, full coagulation screen will not be measured routinely. Blood samples for haemostatic investigations pre- and post surgery will be sent to the Department of Haematology.

During surgery haemostasis will be assessed using ROTEM and Biotrack PT, APTT meter in Theatre 15. If blood loss becomes excessive then samples will be sent from theatre to Department of Haematology for testing.

In view of the diminishing transfusion requirements, aprotinin (trasylo) is no longer used. Occasionally tranexamic acid will be given at the discretion of the anaesthetist in theatre.

Prothrombin time (PT) and activated partial thromboplastin time (APTT) give an estimate of the integrity of the coagulation cascade. A low plasma fibrinogen and elevated D-dimers may indicate a consumptive coagulopathy (e.g. D.I.C.).

5.2 Abnormal coagulation

Likely causes of prolonged prothrombin time include: - graft dysfunction, sepsis, recent transfusion, vitamin K deficiency (if cholestatic) or occasionally donor use of warfarin.

5.3 Correction of coagulation

If the patient is actively bleeding, has required major blood transfusion, or is about to undergo invasive procedures such as liver biopsy or re-operation, attempt to correct coagulation by infusions of fresh frozen plasma, cryoprecipitate and platelet concentrates. Specific coagulation factors may be replaced, on the advice of the consultant haematologist.

If the patient is cholestatic, prolongation of the PT may reflect vitamin K deficiency and be corrected by 10 mg vitamin K.

Outwith the above circumstances, coagulation abnormalities should be monitored, but not routinely corrected.

Specific advice on correction of coagulopathy is given in *Appendix 5*.

5.4 Technical arrangements

A full coagulation screen will be a full blood count (red tube) and prothrombin time, activated partial thromboplastin time, fibrinogen and FDP (green tube). For routine checks after 24 h PT will suffice alone. Samples will be transferred to Haematology and Blood Bank using the Air Tube conveyor system. Products can be ordered direct from BTS.

5.5 Transfusion

There is no requirement for transfusion unless haemoglobin drops below 70g/litre.

5.6 Budd-Chiari Syndrome

Patients transplanted for the Budd Chiari syndrome are kept anticoagulated with intravenous Heparin, and subsequently with Warfarin once oral medication becomes possible and condition is stable.

5.7 Haemophilia

Patients transplanted for Hepatitis C with haemophilia will have had Factor VIII infusion before and during surgery. Factor VIII levels will be monitored by haematology staff for first few post-op days, anticipating a return to normal. Supranormal values should be avoided to minimise thrombosis risk.

5.8 VTE Prophylaxis

Patients will have prophylaxis against thromboembolism following surgery with sub-cutaneous heparin 5,000 units.

All other in-patients will follow the protocol used in the ward 205 for liver patients (*appendix 6*)

Please Note: TED stockings should be prescribed in the drug kardex if there is a contraindication then it should be scored out and the contraindication explained.

6. **CONTROL OF INFECTION**

6.1 General Measure

Current policy for avoidance of transmission of HAI can be found on the intranet and should be adhered to at all times.

<http://intranet.lothian.scot.nhs.uk/Directory/InfectionPreventionAndControl/Pages/NHSLothianInfectionPreventionandControl.aspx>

Although transplanted patients are not barrier nursed on either the Intensive Care Unit or the ward, care should be taken in examining and treating them to avoid unnecessary contamination. Cross-infection particularly with methicillin resistant *Staphylococcus aureus* (MRSA), *Clostridium difficile*, Carbapenamase Producing Enterobacteriae and Norovirus can be major problems, which may be minimised by hand washing before and after examining patients. Alcohol hand gel may be used unless *C. difficile* or Norovirus is a concern in which case soap and water must be used.

- Alcohol hand gel should be used when entering and leaving patient areas.
- Sterile technique should be used in manipulation of drains.
- The naso-gastric tube should be removed at the earliest opportunity.
- Alcohol hand gel and plastic aprons are available outside every room.

6.2 Infection risk

The problems of infection in liver transplant patients are:

1. Preoperatively the patients are ill, frequently malnourished and may have significant infection already. Unusual sites of infection, especially fluid collections (ascites, pleural effusion) and unusual or multiple aerobic or anaerobic organisms are common.
2. Use of broad-spectrum antibiotics selects resistant organisms both in the individual patient and in the unit as a whole.
3. Postoperatively, patients are immunosuppressed and have multiple sites for microbial colonization and invasion.
4. Antibiotics may interact with a number of other drugs, in particular ciclosporin and tacrolimus.

6.3 MRSA , CPE& VRE

MRSA, CPE and VRE (methicillin resistant staphylococcus aureus and vancomycin resistant enterococcus) are of increasing concern, and are of particular relevance to SLTU, where patients have been transferred from other hospitals, have undergone surgery, and are immunosuppressed. In addition to the stringent measures outlined above, all patients will be screened for MRSA carriage on arrival in SLTU.

6.4 PROPHYLAXIS

Note also: Lothian UHD Antimicrobial Prescribing Guidelines via Microguide app on your phone or <https://cms.horizonsp.co.uk/viewer/lothian/adult> and BNF 5.5.1. (pencillins) for detailed comments on penicillin allergy and syndromic treatments

6.4.1 Antibacterial

Antibiotic prophylaxis is Amoxicillin 1g, Gentamicin 2mg/kg and Metronidazole 500mg at induction and Amoxicillin 1g and Metronidazole 500mg at 8 hours

For patients with penicillin allergy Ciprofloxacin 400 mg + Vancomycin 1 g is prescribed at induction and at 12 hours). Metronidazole is required for patients requiring a roux en y.

If known to be MRSA positive at any time add vancomycin (1g slow intravenous infusion over 1.5h) at time zero.

If major intra operative blood loss has occurred, co-amoxiclav 1.2g IV should be given post-op on arrival in ITU.

Routine prophylaxis for cholangiography will comprise gentamicin 2mg/kg iv and 1 g amoxicillin iv (or if penicillin allergic ciprofloxacin 200mg plus metronidazole 500mg).

Patients will receive co-trimoxazole 480 mg daily as prophylaxis against pneumocystis, commencing on oral intake and continued for three months. For the cotrimoxazole allergic patient desensitisation should be considered (*appendix 7*). If this is not practicable dapsone 100mg daily (reduce to 50mg in severe renal impairment) may be used.

Pentamidine via nebuliser should be reserved as third line option. This is prepared in the pharmacy isolation unit and therefore can only be obtained during pharmacy working hours.

The consultant microbiologist on call should be consulted about specific prophylaxis for resistant organisms.

6.4.2 Anti-fungal

Anti fungal prophylaxis will comprise fluconazole 100 mg orally or IV for 3 months.

6.4.3 Anti-viral

6.4.3.1 CMV

High risk recipients (i.e. CMV negative patients receiving a CMV positive donor organ), and all re-transplants (except early re-transplants), will receive oral valganciclovir 900mg (adjusted for renal function) once daily commencing at day 7 and continued until at least 3 months post-transplant (6 months if patient is taking MMF)

CrCL (ml/min) (Cockcroft & Gault)	Valganciclovir tablets
≥ 60	900mg once daily
40-59	450mg once daily
25-39	450mg every 2 days
10-24	450mg twice weekly
< 10	Use oral solution

Dose adjustment for renal function

6.4.3.2 HBV

Patients transplanted for hepatitis B will normally have undetectable viral replication, as indicated by undetectable HBV-DNA in serum, either as a result of previous seroconversion or as a result of recent administration of an oral antiviral.

Evidence published in late 2017 now demonstrates that the use of hepatitis B immunoglobulin is no longer required to prevent recurrent hepatitis B in the context of potent oral antivirals. Tenofovir 245 mg daily or Entecavir 0.5 mg daily should be continued following liver transplantation indefinitely. If egfr <60 then Entecavir should be used and if the patient is not on an antiviral entecavir 0.5mg should be commenced immediately (within 24-48 hours) following transplantation.

In patients infected with HDV (delta virus) it is very important to prevent HBsAg production as HDV infection requires HBsAg. Therefore HBIg should be used. The

administration of HBIg should be 5000 units IV over 5 hours during the transplant operation, on days 1,3 ,and 5 post-operatively and thereafter if anti-HBs titre falls below 100 units. HBIg is available from pharmacy (out of hours contact the on-call pharmacist via switchboard) in the form of Hepatect. This should be infused intravenously at a rate of 0.1mg/kg/hr for 10 minutes and if tolerated the rate can be doubled every 10 minutes to a maximum of 1ml/kg/hour. As it is unclear how long HDV can survive in peripheral blood mononuclear cells use of an anti-HBc positive donor is not recommended.

The use of an anti-HBc positive graft in a recipient without prior exposure to hepatitis B (anti-HBc negative) will require the recipient to receive lamivudine 100mg daily long term as prophylaxis. HBIg is not required. The transplant coordinators will highlight the use of an anti-HBc graft in a non-immune recipient (anti-HBc and anti-HBs negative). Vaccination with HBsAg may be considered after the first year.

6.4.3.3 HCV

The new oral anti-virals are extremely well tolerated and it is possible that a patient admitted for liver transplant is on treatment. This treatment should continue following transplantation if at all possible. A HCV RNA pcr test should be sent within the first 24 hours of admission to virology.

The efficacy of new agents allow HCV negative recipients to be transplanted with a HCV positive graft. HCV pcr should be checked at day 7 and if positive Dr Bathgate or Professor Hayes informed to arrange treatment (see appendix 14 for further information).

6.4.3.4 HEV

Hepatitis E infection following liver transplant is becoming more recognised. It is important to request HEV RNA in addition to serology as immunosuppression may prevent an antibody response. Any unexplained rise in ALT could be as a result of HEV infection. Strategies around treatment of chronic HEV infection continue to be developed and include reduction in immunosuppression and a course of Ribiviran.

6.5 TREATMENT

6.5.1 Anti-bacterial

A consultant microbiologist (usually Dr Ian Laurensen) will advise on treatment of suspected or proven infections. If sepsis is suspected (*appendix 8*) cultures of blood (peripheral and from central and arterial lines), urine, and drain fluid (if present) should be taken. Recent microbiology reports should be reviewed.

The antibiotic regime for suspected sepsis where the organism is unknown is IV gentamicin 2mg/kg, amoxicillin 1g 8 hourly and metronidazole 500mg 8 hourly. If renal impairment piperacillin/tazobactam 4.5g 8 hourly. For penicillin allergic patient: vancomycin as per renal function, ciprofloxacin 400mg 12 hourly with metronidazole 500mg 8 hourly

6.5.2 Anti-fungal

The protocol for anti-fungal therapy in ITU can be accessed via the hospital intranet. http://intranet.lothian.scot.nhs.uk/Directory/CriticalCare/Infection%20and%20sepsis/Antifungal_Guidelines%20UPDATED%202017.pdf

Note that in transplant patients high dose fluconazole is not generally used, both because of the likelihood of resistance from use of fluconazole for prophylaxis, and because of likelihood of interaction with tacrolimus.

6.5.3. Anti-viral

CMV may replicate in several sites, including the lung, liver and GI tract.

If active CMV infection is suspected, send to RIE Virology:

1. One 7ml anti-coagulated EDTA blood tube for detection of CMV DNA in blood by PCR.
2. Fresh tissue (i.e. not in formalin) eg from liver, colorectal or gastric biopsies for CMV PCR (following discussion with RIE Duty Virologist on x26086 or bleep 5981).

NB Tissue in formalin eg, liver, colorectal or gastric biopsies (to look for inclusion bodies on light microscopy) should be sent to RIE Pathology.

The CMV PCR assay is carried out on Tuesday and Friday mornings. Thus, samples for the assay must reach RIE Virology no later than Monday and Thursday afternoons. If CMV is detected by the assay a decision about whether this is viraemia or CMV disease should be made. If CMV disease is suspected, EDTA blood samples should be tested twice weekly by CMV PCR and patients commenced on IV ganciclovir 5 mg/kg bd

(adjusted for renal function; discuss with Pharmacist, bleep 5132). Therapy is continued until 2 CMV PCR-negative samples have been obtained a few days apart at which time 1-3 months of prophylactic oral valganciclovir should be considered to guard against relapse of CMV disease. Alternatively, if clinically well, patients suffering active CMV infection can be converted from IV ganciclovir to oral valganciclovir 900 mg twice daily (adjusted for renal function see table) Treatment with oral valganciclovir rather than iv ganciclovir may be considered in CMV disease but is more likely to be advised in CMV viraemia along with concomitant reduction in immunosuppression.

CrCL (ml/min) (Cockcroft Gault)	Valganciclovir tablets
≥ 60	900mg twice daily
40-59	450mg twice daily
25-39	450mg once daily
10-24	450mg every 2 days
< 10	not recommended- discuss with pharmacist

Dose adjustment for renal function

If ganciclovir (or valganciclovir) fails to control the CMV infection (as manifest by rising CMV levels in blood), second line therapy (and ganciclovir resistance testing) should be considered in liaison with RIE Duty Virologist.

7. **IMMUNOSUPPRESSION**

Standard starting immunosuppression regime is given in appendix 10.

Tacrolimus will be commenced on the first post operative day unless there are significant concerns over renal function when there may be a delay in commencement. The starting dose of Tacrolimus is Adoport 2mg bd if less than 70kg and 3mg bd if over 70kg. The starting dose of Ciclosporin is Neoral 4 mg/kg bd.

These dosages should be halved in patients with renal impairment.

7.1 **CALCINEURIN BLOCKER (TACROLIMUS/CICLOSPORIN)**

7.1.1 **Introduction**

The primary immunosuppressive drug will be one of the calcineurin blockers **Tacrolimus** or **Ciclosporin**. Tacrolimus is available as Adoport/Prograf (twice daily) and Advagraf (once daily). Prograf is to be prescribed following liver transplantation at a dose of 2mg bd for patients less than 70kg and 3mg bd for over 70kg.

Ciclosporin is to be prescribed as Neoral.

7.1.2 **Dosing**

The dosage of Tacrolimus or Ciclosporin must take account of not only the blood concentration, but also the time since transplant, the history of rejection and the side effects, particularly the presence of renal impairment. Toxicity within the recommended blood concentrations can occur.

The dose of immunosuppressive drugs should take account of the relative risks of rejection – the high risk patients are those with a previous history of rejection, younger patients, females and those transplanted for autoimmune diseases e.g. autoimmune hepatitis and primary biliary cirrhosis. Severely malnourished patients and those with renal failure have a lower risk of rejection.

7.1.3 **Recommended trough blood levels**

7.1.3.1 **Tacrolimus**

0 to 6 months	5 - 12 µg/l
After 6 months	4- 10 µg/l

7.1.6.3 Ciclosporin

0 to 6 months 100 - 150 µg/l

After 6 months 70 - 100 µg/l

7.1.4 Dosage Adjustment

If patient has Tacrolimus/Ciclosporin concentration too high or too low, consider the reason prior to adjusting the dose, e.g.:

- Tacrolimus/Ciclosporin too high:
 - Did the patient take Ciclosporin/Tacrolimus on the day of the assay?
 - Has the patient taken any new drugs?
- Tacrolimus/ Ciclosporin too low:
 - Is the patient compliant?
 - Is there impaired absorption? Vomiting or diarrhoea?
 - Has the patient taken any new drugs?

If adjusting dose, increase or decrease by approximately 20%

7.1.5 Tacrolimus/Ciclosporin toxicity

Warning evidence of Tacrolimus/Ciclosporin toxicity:

Headaches, paraesthesia, tremor, fits, nausea, vomiting, diarrhoea, hypertension, hyperkalaemia, renal impairment, arthralgia, diabetes mellitus

7.1.6 Drug Interactions

Drug interactions with Tacrolimus/Ciclosporin

Assume any drug may interact with Tacrolimus/Ciclosporin until you know it does not. If in doubt, contact SLTU pharmacist (Bleep 5132) and monitor U&Es, creatinine and blood Tacrolimus/Ciclosporin concentrations at least 2 x weekly.

7.1.6.1 The following drugs are known to increase Tacrolimus/Ciclosporin concentration (anticipate toxicity and reduce dose or be guided by blood Ciclosporin/Tacrolimus concentrations measured < 1/52 after starting medication).

- amiodarone
- anti-retroviral therapy
- clarithromycin
- danazol
- diltiazem
- erythromycin
- fluconazole (> 200 mg/day)
- itraconazole
- ketoconazole
- nifedipine
- progestogens
- oral anti-HCV therapy

7.1.6.2 The following drugs reduce Tacrolimus/Ciclosporin concentration (anticipate increase requirements but be guided by blood Tacrolimus/Ciclosporin concentrations measured < 1/52 after starting medication).

- carbamazepine
- caspofungin
- griseofulvin
- phenobarbitone
- phenytoin
- primidone
- rifampicin

7.1.6.3 Anti-retroviral therapy: several of the drugs used for HIV infection interact with CNIs. Often patients require only once weekly dosing with Tacrolimus, (however be aware certain drugs may also *reduce* the Tacrolimus concentrations).

Patients transplanted who are HIV positive and on anti-retroviral therapy will be managed jointly with Dr Daire O'Shea from the Regional Infectious Diseases Unit at WGH.

7.1.6.4 The following drugs increase the risk of hyperkalaemia

- potassium-sparing diuretics
- ACE inhibitors/ angiotensin II antagonists – lisinopril, losartan etc

7.1.6.5 The following drugs increase risk of nephrotoxicity
(monitor urea + creatinine 2 x week initially).

- | | |
|------------------|--------------------------|
| – aciclovir | – NSAIDs |
| – amphotericin | – neomycin |
| – co-trimoxazole | – vancomycin |
| – ganciclovir | – valganciclovir |
| – gentamicin | – Any nephrotoxic drugs. |

7.1.7 Tacrolimus in patients with anaemia/hypoalbuminaemia

Because the drug is highly red blood cell and protein bound, increased efficacy/toxicity for a given whole blood concentration will occur if there is anaemia or hypoalbuminaemia.

7.1.8 Generic tacrolimus/ciclosporin

There are now a number of generic tacrolimus and ciclosporin formulations available. It is important to prescribe Prograf and Neoral by name to ensure that the correct formulation is given to maintain appropriate calcineurin levels.

See MHRA Drug Safety Update

<http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON155756>

7.2 BASILIXIMAB

This interleukin-2 receptor antagonist may, in exceptional circumstances, be given in elective patients (except fulminants) with serum creatinine > 150 micromol/l or eGFR < 40 ml/min. The first dose (20mg) will be given within the first 24 hours after transplantation. The second dose (20mg) will be given on Day 4. The drug is no longer on the formulary and a non-formulary request will be required for its use. Consideration should be given in recipients with a risk of acute rejection despite poor renal function e.g. young, well-nourished or autoimmune indication.

Mycophenolate Mofetil (MMF) will be given instead of azathioprine commencing at 500mg bd and increasing to 1g bd.

Tacrolimus will be commenced on day 7 aiming for trough levels 4-7.

7.3 CORTICOSTEROIDS

- 7.3.1 Intravenous Hydrocortisone 100mg bd by bolus injection starting immediately post-operation and stopping when oral intake established.
- 7.3.2 Oral Prednisolone 20mg per day starting once oral intake established. The non-enteric coated 5mg tablets will be used. The dose will be reduced monthly by 5mg increments every 3 weeks and discontinued at three months post-op. Exceptions to this are:
- patients transplanted for autoimmune hepatitis who should continue 5mg/day indefinitely to decrease risk of disease recurrence.

This regime is flexible and may require alteration according to degree of rejection and corticosteroid side effects.

While the patient is receiving corticosteroids, ranitidine 150mg bd orally or 50mg tid IV will be given as prophylaxis against stress ulceration.

7.4 AZATHIOPRINE

- 7.4.1 1 mg/kg/day (rounded to nearest 25mg tablet) once daily when oral intake established.
- 7.4.2 A transplant clinician may prescribe IV Azathioprine for patients requiring prolonged intubation. The dose is 1 mg/kg/day once daily and continued until oral intake established. Note - IV Azathioprine is made up in pharmacy and must be requested in working hours.
- 7.4.3 Marrow suppression: Azathioprine doses may be reduced according to the peripheral neutrophil (NPL) and platelet counts, which often remain low post operatively.

The dose should be adjusted to the formula -

NPL	<1.0 x10 ⁹ /L:	0.5 mg/kg
NPL	< 0.5 x10 ⁹ /L:	stop
Platelets	40 – 60 x10 ⁹ /L:	0.5 mg/kg
Platelets	< 40 x10 ⁹ /L:	stop

7.5 GRAFT REJECTION (see *appendix 10*)

Decisions on treatment of rejection will be made in consultation with the consultant hepatologist. If acute (cellular) rejection is suspected, e.g. fever, jaundice, elevated transaminases; a liver biopsy will be performed.

If acute rejection is confirmed, treat as follows –

- Mild: Observe
 - Moderate/Severe Methylprednisolone 1g /day for 3 days
-
- If clinical and biochemical improvement, simply observe and recommence reducing regimen of oral prednisolone starting at 20mg.
 - If no improvement, re-biopsy around 7 days post treatment.
 - If continuing rejection, repeat above methylprednisolone treatment.
 - If rejection recurs/persists after 2 cycles of methylprednisolone -
 - a) Ensure diagnosis is correct
 - b) If on ciclosporin, convert to tacrolimus.

8. PAIN AND ANXIETY

Post-operative pain will be controlled initially by fentanyl or morphine 1-5 mg/h. If prolonged administration required, use alfentanyl, as less accumulation will occur. Fentanyl or morphine boluses in intubated patients may be useful for physiotherapy and other painful procedures. The patient will usually be converted to patient controlled analgesia (PCA) on 1st post operative day. Paracetamol 1g regularly and oxycodone. if required will be written up when the PCA is no longer required.

Anxiety and restlessness should be treated by intravenous midazolam (0.5-1 mg/hr) or low dose propofol (3-10 ml/hr) once cause of restlessness such as pain, hypoxia, displaced endotracheal tube or blocked urinary catheter have been excluded.

9. **NUTRITION**

9.1 **Enteral nutrition**

Patients that have been identified as being well nourished in the pre –operative assessment usually are able to eat within 2 to 3 days of surgery, and usually diet and/or nutritional supplements are adequate to meet their nutritional requirements. In cases where resumption of oral diet is delayed beyond 3 days, e.g. by prolonged ventilation and in cases with the patient being identified as being moderately or severely malnourished on their pre-operative assessment, enteral feeding should be started in ITU and continued until dietetic assessment indicates that the patient can meet their requirements adequately from oral diet and/or nutritional supplements. Certain patients with severe malnutrition pre-operatively will have had a feeding jejunostomy inserted at time of their transplant. Enteral feeding by this route is according to protocol

9.2 **Parenteral nutrition**

Parenteral nutrition will be reserved for patients unable to be fed enterally e.g. because of prolonged ileus, gastrointestinal bleeding or diarrhoea. In most patients standard regimes will be appropriate. These will be arranged with pharmacy in collaboration with the nutrition team. In patients with poor graft function the nitrogen content of the feed will be reduced, and in patients with persistent sodium retention and ascites, the sodium content of the feed will be kept to a minimum. Parenteral feeding will be via central venous route using a newly placed catheter dedicated to feeding alone.

10. LIVER FUNCTION

10.1 Investigations of abnormal liver function

Abnormal liver function in the early post operative phase may be due to reperfusion injury, ischaemia, bacterial or viral infection, rejection, biliary obstruction, drug hepatotoxicity and cholestasis secondary to previous liver injury or non-hepatobiliary infection. (*Appendix 11*)

Patients may require ultrasound plus Doppler, CT scan, liver biopsy, cholangiography and/or angiography. Patients may deteriorate rapidly, and therefore these investigations may require to be undertaken at short notice. The results of the investigations often require immediate intervention or change in therapy.

10.2 Vascular complications

The first line investigation for suspected vascular problems is doppler ultrasound. Suspected abnormalities will be followed up with contrast triple phase CT. MRA may also be helpful – options should be discussed with the “duty” radiologist. Invasive angiography will rarely be required. Hepatic artery thrombosis usually requires retransplant. Hepatic artery stenosis should be treated with aspirin and/or low dose heparin. Doppler ultrasound will be requested by ITU staff on the first post-op day to check flow in the hepatic artery, portal vein and hepatic veins/IVC anastomosis.

An abnormal or equivocal arterial signal on Doppler is an indication for contrast CT.

10.3 Biliary complications

Biliary leakage, diagnosed by clinical evidence of bile-staining of abdominal drain fluid, ultrasound and/or cholangiography, may be dealt with conservatively or may require surgical correction. Conservative treatment includes antibiotics. If cholangitis or biliary abscess is diagnosed or suspected, possible drainage of either/both of the biliary tree (by means of percutaneous external biliary drainage or endoscopic stent insertion \pm sphincterotomy) and any collection (by ultrasound guided external drainage).

Biliary obstruction, also diagnosed by ultrasound and/or cholangiography, is rare in the early post-operative phase. Obstruction caused by sludge may respond to ursodeoxycholic acid, or may require endoscopic sphincterotomy and duct

clearance. Biliary anastomotic strictures can be dealt with non-operatively by endoscopic or percutaneous balloon dilatation and/or stent insertion, or operatively by conversion to a choledochojejunostomy. Removable metal stents placed at ERCP are now available for anastomotic strictures. Non-anastomotic or multiple biliary strictures are normally a consequence of ischaemia. A Doppler ultrasound to assess hepatic artery is mandatory. *Note that all invasive cholangiography, and any liver biopsy in patients with current or previous cholangitis or biliary obstruction, requires prophylactic antibiotics (See section 6).*

10.4 Liver Biopsies

Rejection may be impossible to distinguish from ischaemia or infection (especially viral) without a liver biopsy. Biopsy should be performed before altering the anti-rejection therapy. Acute cellular graft rejection, diagnosed by histology, usually responds to corticosteroids (see section 7.3).

Professor Harrison or Dr Bellamy in the Department of Pathology must be informed that a biopsy is planned. If the prothrombin time is more than 5 seconds prolonged and the platelet count is less than 60,000, fresh frozen plasma and platelet concentrate should be administered.

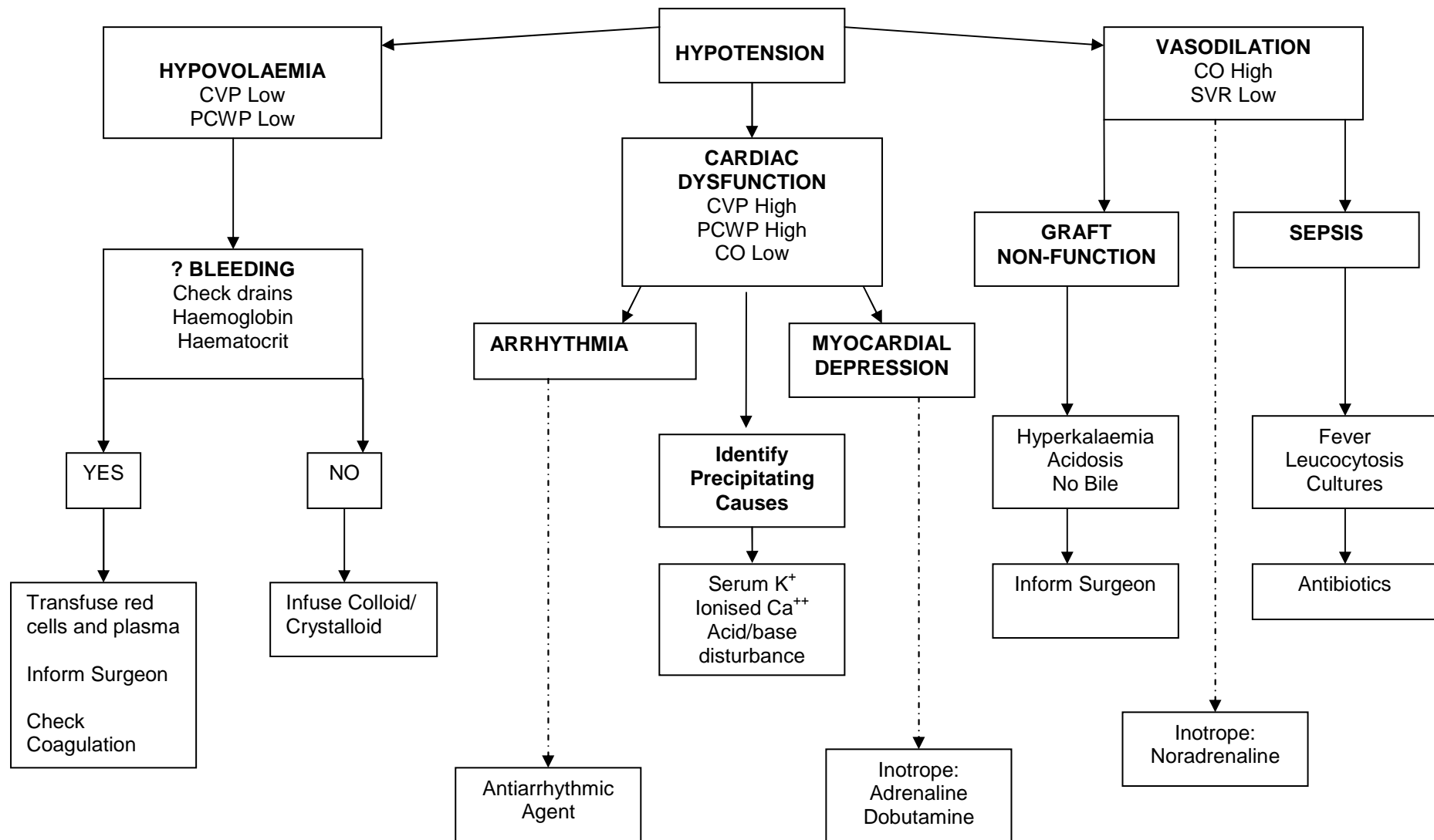
An adequate needle core must be obtained by an experienced operator. The specimen should be placed in Formal saline and taken to the Department of Pathology, for the attention of Prof Harrison or Dr Bellamy. Every effort should be made to deliver the sample to Pathology before 12 noon to allow a report to be issued that day. **If there is a history of cholangitis, liver biopsy should be covered by prophylactic antibiotics** (see section 10.3 and section 6).

If the patient has received a segmental (“cut down” or split) graft, the biopsy must be undertaken using ultrasound guidance

APPENDICES

APPENDIX 1

Algorithm for management of hypotension.



APPENDIX 2

Blood results sheet for first 24 hours post op

Patient	Liver Transplant
Label	Blood Results Sheet (1st 24 Hours)

All boxes should be completed in an uncomplicated case.

Additional blood tests may be required eg, following blood products during active bleeding

Do "Morning Bloods" at appropriate time, usually 18 hour sample

Time Taken										
Hour Post-op	0	1	2	3	4	5	6	12	18	24
H ⁺										
PaCO ₂										
SBC										
BE										
FiO ₂										
PaO ₂										

Lactate										
Glucose										
BM										

Na ⁺										
K ⁺										
Ca ²⁺										

CO ₂	
Urea	
Creatinine	

CO ₂	
Urea	
Creatinine	

Hb (Co-ox)										
Hb (Lab)										
Platelets										
PT/control										
APTT/control										
Mix										
Fibrinogen										
D-dimer										

Products										
Time	Th									
FFP										
Platelets										
Cryo										
RCC										
Other										

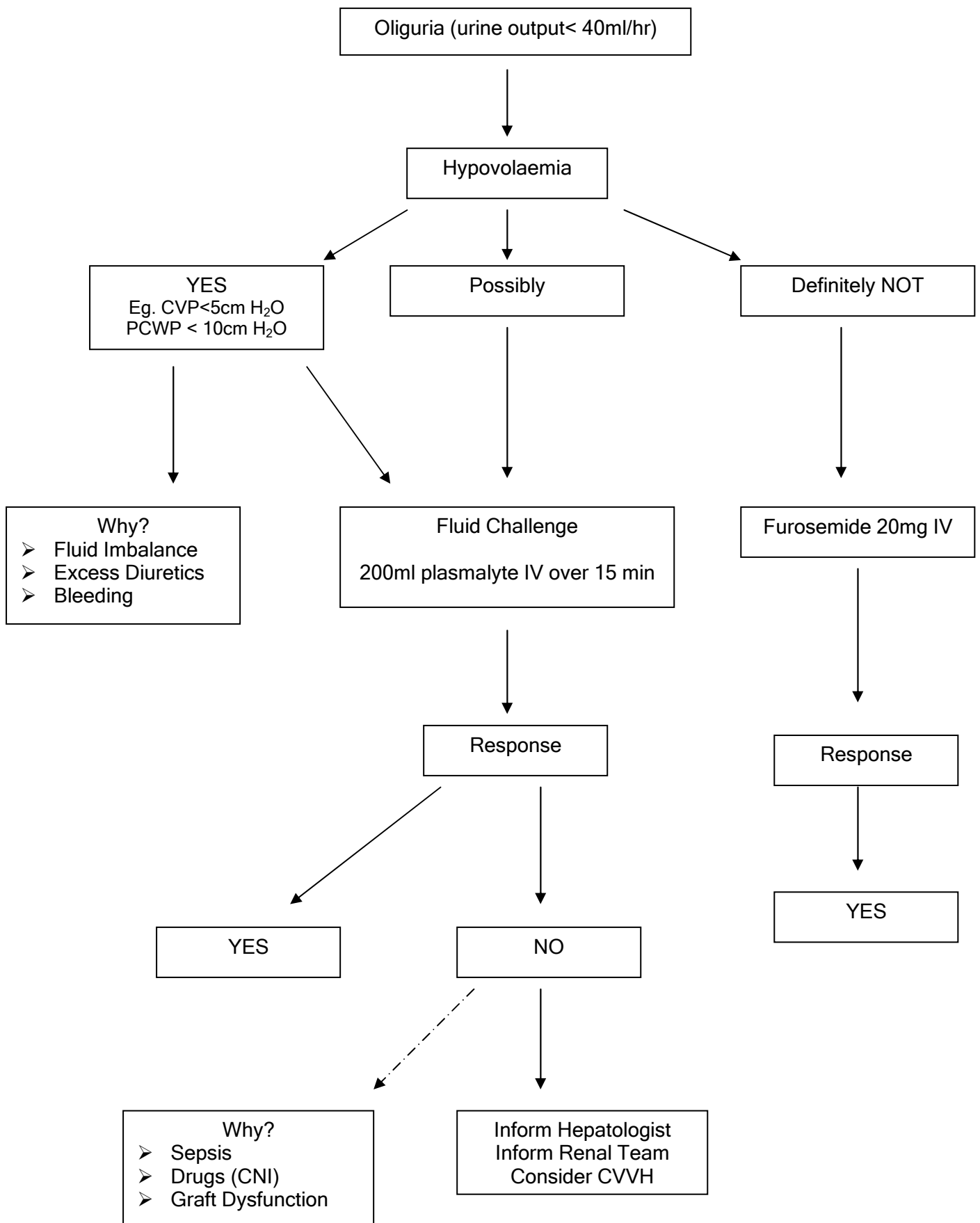
Bilirubin	
ALT	
GGT	
Alk Phos	

Bilirubin	
ALT	
GGT	
Alk Phos	

Ciclosporin/ Tacrolimus Level	
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APPENDIX 3

Algorithm for management of oliguria.



APPENDIX 4

Nephrotoxic drugs used in liver transplant recipients.

Potentially nephrotoxic drugs in liver graft recipients or patients with liver failure.

- Aciclovir
- CiclosporinGanciclovir/Valganciclovir
- Gentamicin
- NSAIDs
- Penicillamine
- Radioiodinated contrast medium
- Tacrolimus
- Vancomycin

A. Active bleeding/major transfusion

PTR > 1.5	-	FFP 2 units
Platelets < 40,000	-	platelets 5 units
Fibrinogen < 1.0	-	cryoprecipitate 10 units

B. Pre-procedure (reoperation, liver biopsy, ERCP, PTC)

PTR > 1.2	-	FFP 2 units
Platelets < 80,000	-	Platelets 5 units

C.

Volume overload Risk of pulmonary/cerebral oedema Continued bleeding despite measures in A	Discuss with consultant haematologist on call re use of specific coagulation factors
--	---

APPENDIX 6

Venous Thromboembolism Risk Assessment Chart

Ensure initial clotting screen and FBC is filled out prior to completion of chart.

1. Contraindication to Heparin? <div style="display: flex; flex-wrap: wrap;"><div style="width: 50%;"><input type="checkbox"/> Platelets <70 <input type="checkbox"/> INR >2 <input type="checkbox"/> Acute bacterial endocarditis <input type="checkbox"/> severe hyperten. (>230/120) <input type="checkbox"/> HIT</div><div style="width: 50%;"><input type="checkbox"/> Acute/Active bleed <input type="checkbox"/> Neuro/spinal/eyesurgery <input type="checkbox"/> Allergies/hypersensitivity <input type="checkbox"/> Pregnancy <input type="checkbox"/> CVVH</div></div>	<div style="border: 1px solid black; padding: 5px;">Patient Addressograph Name:</div> <div style="border: 1px solid black; padding: 5px; margin-top: 5px;">CHI:</div>
---	---

☐ **No** - continue with VTE Risk assessment

☐ **Yes** – consider TEDS
Go to Step 3

2. VTE Risk Assessment. Please Tick.

☐ Age >60
☐ BMI >30
☐ IBD
☐ COCP/HRT
☐ CCF/recent ACS/CVA
☐ Metabolic syndrome eg DM
☐ Myeloproliferative disease
☐ (EG Polycythaemia/thrombocytosis)

☐ Cancer
☐ Hospitalisation/immobility
☐ Personal or Family history of VTE
☐ Central venous catheter
☐ Severe acute infection
☐ Varicose veins
☐ Thrombophilias

☐ Two or more Risk Factors

☐ <2 Risk Factors

Dalteparin 5,000 units SC OD
(Less than 46kg 2,500)
(EGFR<30 use minihep)
Maximum 14 days

Early Mobilisation – if not TEDS

3. Contra-indications to TEDS
☐ Massive leg oedema/lymphoedema
☐ Severe PAD
☐ Severe peripheral neuropathy
☐ Major leg deformity
☐ Dermatitis
☐ Pulmonary oedema

4. Please Confirm Prescription
☐ Dalteparin/minihep
☐ TEDS
Signature, Name, Date

First Line

Co-trimoxazole 480 od

Desensitisation can be attempted in patients with a non-severe (grade 3 or less) co-trimoxazole reaction. This should be carried out as soon as possible following OLT. It should **not** be attempted in patients with a grade 4 reaction to co-trimoxazole or other sulfa drugs. Toxicities can be graded as follows in Table 1

Table 1 Grade 1-4 Co-trimoxazole toxicity

Toxicity	Clinical description
Grade 1	Erythema
Grade 2	Diffuse maculopapular rash, dry desquamation
Grade 3	Vesiculation, mucosal ulceration
Grade 4	Exfoliative dermatitis, Stevens-Johnson syndrome or erythema multiforms, moist desquamation

If a minor reaction occurs during the desensitisation regimen, then repeat the same step for an additional day and progress to next step if the reaction subsides. If the reaction worsens or a severe reaction occurs, stop the desensitisation. Consider giving concurrent antihistamine (ie cetirizine 10mg once daily), commenced one day prior to starting the desensitisation regimen. If the reaction worsens or a severe reaction occurs, stop the desensitisation.

Table 2- Co-trimoxazole desensitisation regimen

Step	Dose
Day 1	80mg sulfamethoxazole + 16mg trimethoprim (1ml oral suspension)
Day 2	160mg sulfamethoxazole + 32mg trimethoprim (2ml oral suspension)
Day 3	240mg sulfamethoxazole + 48mg trimethoprim (3ml oral suspension)
Day 4	320mg sulfamethoxazole + 64mg trimethoprim (4ml oral suspension)
Day 5	400mg sulfamethoxazole + 80mg trimethoprim ie 1 x 480mg tablet

Co-trimoxazole oral suspension is 400mg sulfamethoxazole + 80mg trimethoprim per 5ml

Reference:

World Health Organisation. Guidelines on co-trimoxazole prophylaxis for HIV-related infections among children, adolescents and adults. Recommendations for a public health approach. WHO. Geneva 2006 <http://www.who.int/hiv/pub/guidelines/ctxguidelines.pdf>
 BHIVA Treatment of Opportunistic Infection in HIV-seropositive individuals 2011
http://www.bhiva.org/documents/Guidelines/OI/hiv_v12_is2_Iss2Press_Text.pdf

Second Line

Dapsone 100mg od

Consider dose reduction to 50mg od in severe renal dysfunction (Creatinine clearance <10ml/min)

Third Line

Nebulised Pentamidine 300mg every 4 weeks – refer to following guidelines for details of administration.

Administration of Nebulised Pentamidine

Equipment

Pentamidine nebuliser solution 300mg x 1

Salbutamol 2.5mg/2.5ml nebule x 1

NaCl 0.9% 5ml x 1

Nebuliser Compression

ISO-NEB Filtered Nebuliser System (ref 41755) and elephant tubing for pentamidine

Nebuliser chamber and mask for salbutamol

Apron

Gloves

P1 type mask

Pair of goggles

“Do Not Enter” Sign

Method

1. Put patient in dedicated room with window to outside and closed door. Place “DO NOT ENTER” sign on outside of door informing others not to enter.
2. Administer salbutamol nebuliser as per usual practice.
3. Put on apron, gloves, mask and goggles.
4. Prepare nebulising equipment for administration of Pentamidine.
5. Connect ISO-NEB Filtered Nebuliser System to compressor.
6. Place elephant tubing out of open window.
7. Draw up Pentamidine nebuliser solution and add to chamber of ISO-NEB Filtered Nebuliser System.
8. Instruct patient to tight seal around mouthpiece during administration and switch of compressor during treatment if mouthpiece needs to be removed from the mouth.
9. Leave the room.
10. Indicate to the patient to start the compressor.
11. If patient is unable to start the compressor for themselves start it for them then leave the room immediately.
12. Check patient every 5 minutes for 20 minutes until nebulisation is complete. If there is any need to enter the room during administration put on gloves, apron, mask and goggles before entering and switch of compressor immediately on entering the room.
13. Indicate to patient to switch of the compressor and leave the room closing the door behind them.
14. DO NOT ENTER the room for at least 2 hours after the administration of nebulised Pentamidine.
15. Enter the room and dispose of equipment in a clinical waste bag.

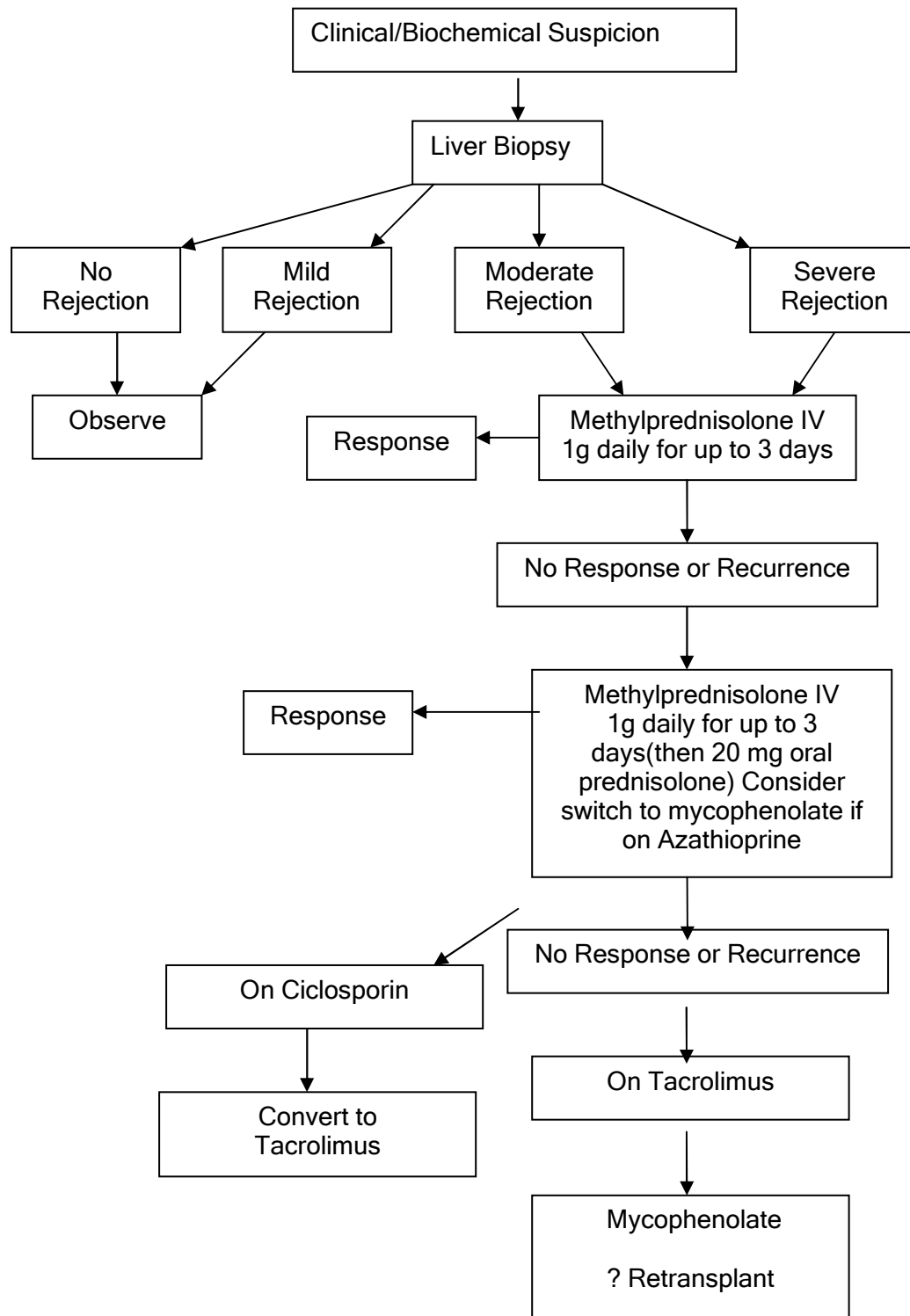
1. Temperature $> 38^{\circ}$ or $< 35^{\circ}\text{C}$
2. Unexplained hypotension or tachycardia
3. WBC $> 10 \times 10^9/\text{l}$, or $< 2 \times 10^9/\text{l}$ where previously normal
4. Unexplained clinical deterioration, especially of conscious level
5. Unexplained deterioration in hepatic function, especially cholestasis
6. Unexplained oliguria

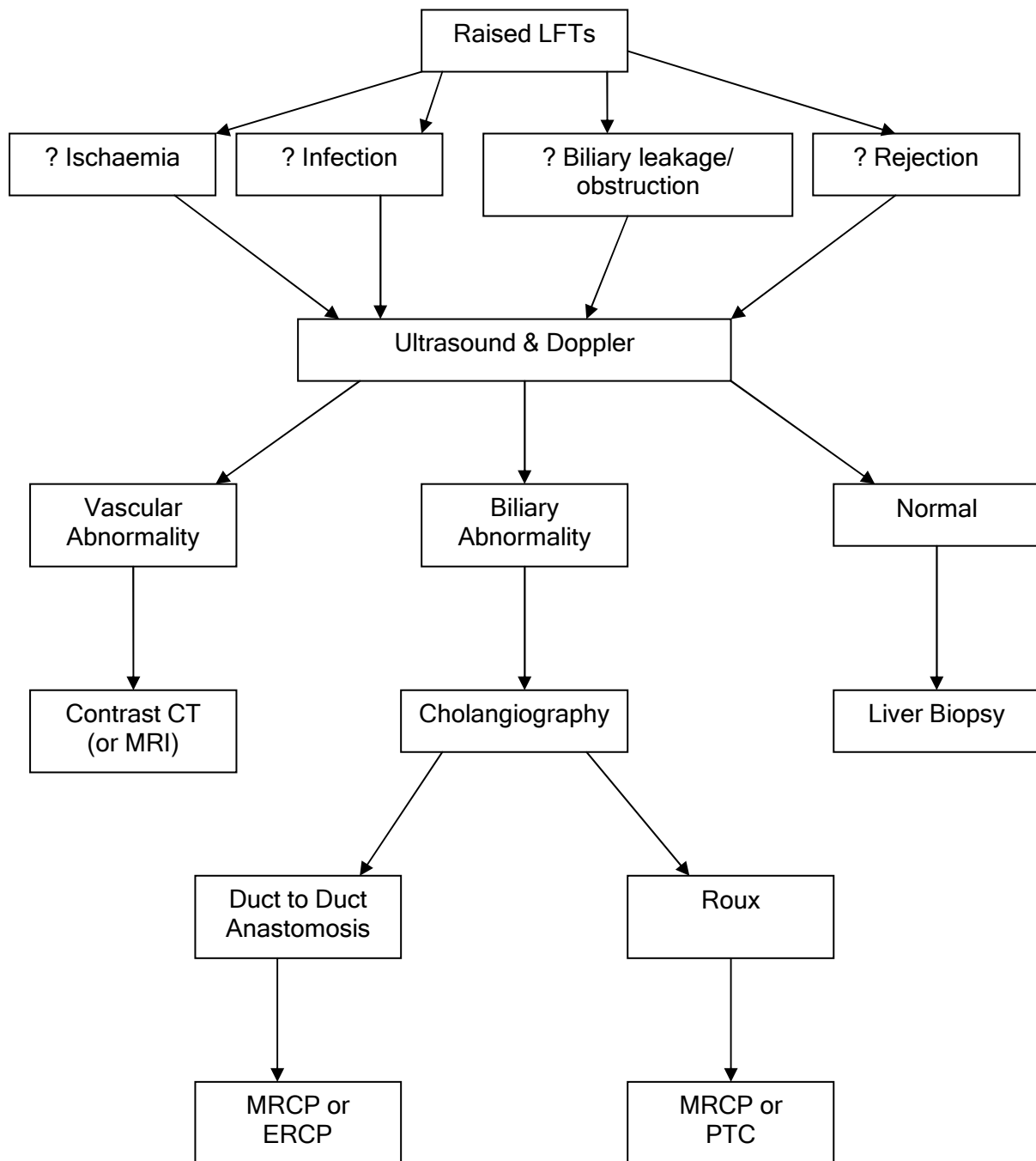
	Intravenous	Oral
Tacrolimus* (Adoport)		4mg total daily if <70 kg 6mg total daily if >70kg
Ciclosporin* (Neoral)		4 mg/kg bd
Corticosteroids		
hydrocortisone	100 mg bd	
prednisolone		20 mg daily
Azathioprine	1 mg/kg daily	1 mg/kg daily
Basiliximab	20mg day 1 and 4	
Mycophenolate Mofetil		500mg bd initially Increasing to 1g bd if tolerated

* *Half dose if renal impairment*

APPENDIX 10

Algorithm for management of graft rejection.





APPENDIX 12 Histocompatibility and Immunogenetics (H&I) support for SLTU

Historically the RIE SNBTS H&I laboratory has provided crossmatching, antibody testing and HLA typing of patients and donors to support the SLTU. Following recent publications and an analysis of local data, the following services will be provided in the future to support the management of patients transplanted within the SLTU:

- 1) DNA from patients and donors will be stored i.e. no HLA typing will be undertaken unless indicated by antibody testing (see below).
- 2) At the time of transplant serum will be screened for HLA antibodies.
- 3) If positive this serum will be tested for the presence of donor specific antibodies (DSA).
- 4) To identify the presence of DSA, HLA typing will be performed on stored donor DNA and patient DNA if necessary.
- 5) For all DSA positive cases the H&I staff will contact the transplant coordinators 1 month post transplant to request a sample to see whether HLA-DSA levels have dropped or persist at the pre-Tx level.
- 6) Results will be reported to the coordinators and the hepatologist managing the patient at the time of testing.

No change should be made to the samples being sent to the H&I laboratory.

Appendix 13 HCV Antibody Positive Donor Management

