Management of patients undergoing liver transplantation

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With reference to:

- EASL Clinical Practice Guidelines: Liver Transplantation 2015
- Evaluation for Liver Transplantation in Adults: 2013 Practice Guideline by the AASLD and the American Society of Transplantation

See also:

Adult liver transplantation: A UK clinical guideline – part 1: pre-operation
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Adult liver transplantation: UK clinical guideline – part 2: surgery and post-operation
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1 Scope

Trust-wide.

2 Purpose

To ensure consistency of clinical care for patients undergoing liver transplantation within a multidisciplinary setting.
To maintain the highest standards of liver transplant management.

(For specifics for acute liver failure please see separate guideline)

3 Contents

4 Abbreviations used

ABG	arterial blood gas
ABPM	ambulatory blood pressure monitoring
Ab	antibody
ACE	angiotensin-converting enzyme
AMR	antibody mediated rejection
anti-HBc	hepatitis B core antibody
art	arterial
ATG	anti-thymocyte globulin
AXR	abdominal x-ray
Aza	azathioprine
bd	twice a day
BMI	body mass index
BNF	British National Formulary
BP	blood pressure
Bx	biopsy
CF	cystic fibrosis
CIT	cold ischaemia time
CMV	cytomegalovirus
CNI	calcineurin inhibitor
CrCl	creatinine clearance
CPM	central pontine myelinolysis
CRP	C-reactive protein
CsA	ciclosporin A
CT	computed tomography
CTPA	computed tomography pulmonary angiogram
Cu	copper
CVC	central venous catheter
CVP	central venous pressure
CVVHD	continuous venous-venous haemodiafiltration
CXR	chest x-ray
d/w	discussed with
DEXA	dual energy x-ray absorptiometry
DM	diabetes mellitus
DNA	deoxyribonucleic acid
DRA	diuretic resistant ascites

DSA	donor specific antibody
EBV	Epstein-Barr virus
ECD	extended criteria donor
ECG	electrocardiogram
EDTA	ethylene diamine tetraacetic acid
eGFR	estimated glomerular filtration rate
ERCP	endoscopic retrograde cholangiopancreatography
FBC	full blood count
FFP	fresh frozen plasma
FK	tacrolimus (Adoport®, Prograf®, FK506)
GFR	glomerular filtration rate
GP	general practitioner
HA	haemagglutination assay
HADS	hospital anxiety and depression scale
HAT	hepatic artery thrombosis
Hb	haemoglobin
HBIg/G	hepatitis B immunoglobulin
HBPM	home blood pressure monitoring
HBs	hepatitis B surface
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
Hct	haemotocrit
HCV	hepatitis C virus
HDV	hepatitis D virus
HDU	High dependency unit
Hep	hepatitis
HIV	human immunodeficiency virus
HPS	hepatopulmonary syndrome
HSV	herpes simplex virus
HT	hypertension
ICU	intensive care unit
ID team	infectious diseases team
IHD	ischaemic heart disease
IM	intramuscular
INR	international normalised ratio
IV	intravenous
LFT	liver function test
LMS	left main stem (coronary artery)
LWL	liver waiting list clinic
MAC	mid-arm circumference
MACE	major adverse cardiovascular event
MASH	Metabolic dysfunction-associated steatohepatitis
MDM	multidisciplinary meeting
MDT	multidisciplinary team
MELD	model for end-stage liver disease
Mg	magnesium
MMF	mycophenolate mofetil
MPAG	mycophenolic acid glucuronide
MRA	magnetic resonance angiography
MRCP	magnetic resonance cholangiopancreatography
MRI	magnetic resonance imaging (scan)

MRSA	methicillin-resistant staphylococcus aureus
Na	sodium
NG	nasogastric
NJ	nasojejunal
NSAID	non-steroidal anti-inflammatory drug
NSBB	non-selective beta blockers
od	once a day
OGD	oesophagogastroduodenoscopy
OLT	orthotopic liver transplant
PA	pulmonary artery
PaO_2	partial pressure of oxygen in arterial blood
PBC	primary biliary cholangitis
PCA	patient controlled analgesia
PJP	pneumocystis pneumonia
PCR	polymerase chain reaction
PN	parenteral nutrition
po	oral
post-op	postoperative/ postoperatively
PPI	proton pump inhibitor
pre-op	pre-operative/ pre-operatively
PSC	primary sclerosing cholangitis
PT	prothrombin time
PTC	percutaneous transhepatic cholangiogram
PV	portal vein
RNA	ribonucleic acid
RWMA	regional wall motion abnormality
sat	saturation
sBP	systolic blood pressure
sc	subcutaneous
sPAP	systolic pulmonary artery pressure
SpR	specialist registrar
ST	specialty trainee
TB	tuberculosis
tds	three times a day
Tc99	Technetium99
TTO	‘to take out’ (medicines to be taken away by a patient being discharged)
Tx	transplant
U&E	urea and electrolytes
UDCA	ursodeoxycholic acid
US	ultrasound scan
UKELD	United Kingdom model for end-stage liver disease
VBD	vanishing bile duct
WCC	white cell count
W/L	waiting list
Zn	zinc

5 Transplant assessment

The aim of transplantation in most cases is to prolong life expectancy. Transplantation is not without risk with an overall 1-year survival of 93%. Therefore, the purpose of transplant assessment is two-fold: to identify the benefit of transplantation (prognosis and symptoms) and to identify any contra-indications to transplantation. The outcome of the assessment process depends on the balance between benefit and risk. Contra-indications are often relative and can result in some debate in the transplant MDT meeting.

5.1 Indications, criteria and contra-indications for liver transplantation

Indications:

Indications and criteria for transplant assessment can be found in detail in the NHSBT guidelines (https://www.odt.nhs.uk/transplantation/tools-policies-and-guidance/policies-and-guidance/; POL195). This document should be consulted regularly as the guidelines are under regular review.

Broadly speaking patients are within criteria for listing if they have a UKELD score ≥49 indicating survival benefit with transplantation or have a variant syndrome e.g. hepatopulmonary syndrome, recurrent cholangitis, intractable pruritus, or polycystic liver disease.

Hepatocellular carcinoma transplant criteria are (on 2 imaging modalities):

- a single tumour ≤5cm; up to 5 tumours all ≤3cm;
- single tumour >5cm and ≤7cm where there is no evidence of tumour progression (<20% increase in volume) and no extrahepatic spread/new nodule formation over a 6-month period.
- Tumours down-staged into criteria according to Duvoux criteria with a score of ≤2 after down-staging.

Variable	Points
Largest diameter (cm)	
≤3	0
3–6	1
>6	4
Number of nodules	
1–3	0
≥4	2
AFP (kU/L)	0
100–1000	2
>1000	3

Locoregional therapy/chemotherapy may be given during this time.

There must be no radiological evidence of vascular invasion and no distant metastasis.

AFP >1000 kU/L contra-indicates liver transplantation.

Downstaging of HCC – see Appendix A of NHSBT document above

Contra-indications:

Most contraindications are relative.

Absolute contraindications:

- Alcohol-related liver disease with active alcohol consumption (consumption of alcohol on the list will result in removal from the list); or repeated nonadherence with advice to abstain; or current use of illicit or non-prescribed drugs; or recent history of cross dependency (other substance abuse in addition to alcohol within the last 2 years). Currently acute alcoholic hepatitis remains a contraindication to transplantation; recent guidelines (Masson et al., 2021, DOI:10.1016/s2468-1253(21)00195-3)
- Illicit drug use: active intravenous illicit drug use; more than one recent incident of unexplained significant nonadherence with any treatment; current failure to comply including the refusal to provide consent for information regarding drug treatment; recent history of cross dependency.
- Porto-pulmonary hypertension with mean pulmonary artery pressure (MPAP) >50 mmHg/right heart failure and no clinical response to medical therapy.
- Current malignancy – current non-hepatocellular carcinoma malignancy excludes liver transplantation in most cases.
- Overall 5-year survival less than 50% taking into account surgical risk and comorbidities. Factors that may affect the risk of transplantation or 5-year survival include the following:

    - Surgical – vessel thrombosis, upper abdominal surgery such as open cholecystectomy
    - Age
    - Obesity, low body mass index, sarcopaenia
    - Diabetes mellitus (especially if long term insulin/end-organ effects)
    - Cardiovascular disease/cerebrovascular disease/peripheral vascular disease
    - Chronic kidney disease
    - Poor functional status
    - Smoking
    - Previous cancer
    - Pulmonary hepatic-vascular disorders (hepatopulmonary syndrome, porto-pulmonary hypertension)

Contra-indications to liver transplantation
(see Millson et al, Frontline Gastroenterology, 2020)
http://dx.doi.org/10.1136/flgastro-2019-101215

Absolute Contraindications	Relative Contraindications
Severe extrahepatic disease with predicted mortality >50% at 5 years including psychiatric disorder	Extensive previous abdominal surgery
Ongoing alcohol misuse	BMI >40 kg/m^2
Active illicit drug use	Poor clinic attendance and/or adherence
HCC outside current UK liver transplant listing criteria	Inadequate social support
Cholangiocarcinoma§	
Active or previous extra-hepatic malignancy†	
Severe irreversible pulmonary disease	
Untreated HIV*	
Ongoing extra-hepatic sepsis*	

§Except for within cholangiocarcinoma pilot transplant programme.
*These contraindications may be temporary and if can be resolved/brought under control such that a good prognosis post-transplant can be anticipated, then do not contraindicate transplantation.
†In cases of previous history of extra-hepatic malignancy, details regarding tumour and stage to be obtained with expert prognostic assessment from relevant specialists to inform decision-making.

Smoking

Smoking increases the risk of vascular complications such as hepatic artery thrombosis after liver transplantation and has negative effects of important co-morbidities such as cardiovascular risk.

In relation to listing for transplantation:

- For those with a diagnosis of a major smoking relating condition, smoking cessation is mandatory prior to listing. Examples of such conditions include ischaemic heart disease, chronic obstructive pulmonary disease, peripheral vascular disease, and stroke.
- For those who do not currently have a major smoking-related condition, smoking cessation is recommended and requested, but not a contraindication to listing.

5.2 Transplant assessment process

Patients will be admitted for a period of transplant assessment based on the referral information provided by an external consultant, or following review in the outpatient department. Currently two to three patients are typically assessed on an outpatient basis each week.

It is helpful if all outside imaging and histology is reviewed prior to the assessment. Direct referrals to the Trust may well require full investigation and work-up, including duplication of scans (see below). Slides should be sent to Dr Sue Davies / Dr Rebecca Brais / Dr Adam Duckworth / Dr Anna Paterson in pathology.

During the assessment, it is the responsibility of the assessing hepatology registrar/senior clinical fellow to perform a detailed history and examination taking into account the indications and potential contraindications to transplantation. **In particular, information should be sought from the GP and referring hospital regarding relevant comorbidity including diabetes, cardiovascular disease and malignancy, as well as a corroborative addiction history**. Specialist input may be needed to determine prognosis and a renal opinion may be necessary in patients with chronic kidney disease (see below), but only after discussion with the consultant hepatologist. The assessing registrar will complete the MDT documentation and will discuss the patient's case at the transplant MDT meeting. It is good practice for the registrar to formulate an opinion before presenting.

The recipient transplant co-ordinator of the week oversees the process. The patient will be provided with detailed information by the transplant coordinator to allow them to make an autonomous decision regarding transplantation. All patients will receive a pre-transplant information booklet and once on the list, they should be contactable by mobile phone.

- Clinical review by the following members of the liver transplant team
  - Liver transplant co-ordinator
  - Hepatology SpR/senior clinical fellow
  - Hepatology/liver transplant dietitian
  - If substance misuse issues, liver transplant mental health nurse, liaison substance misuse team OR another member of the liaison substance misuse liaison psychiatry team.
  - Consultant transplant surgeon
  - Consultant transplant anaesthetist
  - Consultant hepatologist
  - Also seen by liver transplant recipient (member of ALTA; suspended temporarily during COVID-19 pandemic)
- Further additional tests performed as indicated

5.2.1 Laboratory investigations

- FBC, U&Es, LFTs, split bilirubin, calcium, magnesium, phosphate, coagulation screen and INR, lipids, TSH, ferritin plus iron studies, vitamin B_{12} and folate, alpha-1 antitrypsin level, vitamin D level.
- Cu/caeruloplasmin if <50 years
- Alpha-1 antitrypsin phenotype in patients with a level below the reference range
- HFE genotype if ferritin >400 and transferrin saturation >45%
- G&S x 2 (on separate occasions)
- α-fetoprotein
- CA19.9 in patients with primary sclerosing cholangitis
- Liver auto antibodies/ immunoglobulins, anti-tTG IgA
- 10 mls for virology screen (request OLT viral screen, which includes HBsAg, anti-HBs titre, anti-HBcAb, anti HCV, HIV, CMV IgG, HSV IgG, VZV IgG, EBV IgG, toxoplasma

IgG. Request HCV RNA if anti-HCV positive; HBV DNA and anti-HDV if HBsAg positive)
- 30 ml citrated for tissue typing (unless HBsAg positive)
- 10 ml serum sample for tissue typing (unless HBsAg positive)

5.2.2 Renal investigations

- All patients should have a urinalysis and, if proteinuria is demonstrated, a urinary ACR
- If known chronic kidney disease with:
  - MDRDv6 eGFR<30 ml/min, or
  - MDRDv6 eGFR<40 ml/min for ≥3 months

  then consider formal isotope GFR and renal ultrasound scan. The hepatology consultant will advise regarding the need for a formal renal opinion if combined liver-kidney transplantation is being considered.

5.2.3 Cardiac investigations

All patients:

1. Careful history to identify potential IHD symptoms (angina, disproportionate exertional dyspnoea, syncope, palpitations)

2. Routine ECG and transthoracic echocardiography

3. Echocardiography should include the following, which must be specified for all external studies:

    a. Quantitative estimation of LV ejection fraction, noting that EF<60% the setting of end-stage liver disease is an independent predictor of MACE and reduced survival.
    b. Assessment for raised left ventricular filling pressure (on 2016 ASE/EACI and current BSE criteria).
    c. Assessment for raised RV systolic pressure, quantifying probability of pulmonary hypertension as low, intermediate or high (on 2016 ASE/EACI and 2018 BSE criteria).
    d. Assessment of RV function, to include fractional area change when probability of pulmonary hypertension is intermediate or high, or if any suggestion of RV impairment (2020 BSE criteria)

4. Consult cardiologist if:

    a. IHD history when management not optimised.
    b. IHD symptoms, aiming to confirm diagnosis and optimise secondary prevention.
    c. LV or RV dysfunction on echocardiogram:
        i. to confirm echocardiographer's findings since either may contraindicate transplant
        ii. to establish diagnosis and appropriate long-term treatment and follow-up.
    d. Clinically significant dysrhythmia (e.g. refractory uncontrolled AF, symptomatic or high-risk heart block, sustained junctional rhythm, etc).

e. Mean aortic gradient >30mmHg, or other significant valvular / LVOT obstruction: stress testing may be indicated to assess haemodynamic significance.
f. High echocardiographic probability of pulmonary hypertension: requires RHC, which may be performed at referring hospital (see 6. below)

5. Further testing may be indicated if:

   [see algorithm in Appendix 25]

   a. Suspected but unconfirmed symptomatic IHD, e.g. angina, pre-syncope, disproportionate dyspnoea: CTCA is usual first choice; MPI or DSE if unsuitable for CTCA.

   b. High aggregate risk: multiple cardiac AND other risk factors that combine to make the candidate a very poor but not clearly prohibitive perioperative risk. Additional testing should not be done unless the patient is considered an acceptable risk in all other respects. CTCA is usual first choice:

      i. If CTCA shows high-risk obstructive disease (>50% LMS, >70% proximal LAD, or three-vessel stenoses) transplant perioperative risk is prohibitive.
      ii. If patient is unsuitable for CTCA (AF/tachycardia, significant renal impairment, heavy calcification, intolerant of position), MPI or DSE may be considered.
      iii. Incremental risk associated with inducible ischaemia would be considered prohibitive without requiring coronary angiography. A negative test would allow transplant.

   c. If echocardiogram suggests high probability of pulmonary hypertension or shows any evidence of RV dysfunction (reduced fractional area change), referral for RHC is required. This is to differentiate pulmonary arterial hypertension ('true' portopulmonary hypertension) from pulmonary venous hypertension caused by fluid overload or HFNEF, since these three conditions have different treatments and prognoses.

      RHC should include measurement of PCWP and cardiac output, and calculation of pulmonary vascular resistance (PVR) and transpulmonary gradient (TPG). Cardiac output is vital in determining diagnosis, management and prognosis. Left heart catheterisation, allowing measurement of diastolic pressure gradient (DPG), is sometimes needed if the cause of pulmonary hypertension remains uncertain.

   d. Aortic stenosis and hypertrophic LV outflow tract obstruction: when estimated mean gradient is >30 mmHg, stress testing may be indicated to assess haemodynamic significance – consult cardiologist.

   e. Testing outside these criteria should be discussed with cardiology team

6. Significant global LV or RV dysfunction, or PA mean >35 mmHg normally contraindicate liver transplantation, although this may be reconsidered after treatment.

7. Combined liver transplant and CABG or AVR, or pre-transplant TAVR, have been successful in other centres and development of these options for selected patients may be considered.

5.2.4 Dietetic assessment

Nutritional Assessment for LTA

An individualised assessment will be undertaken by a hepatology dietitian, to include:

Physical assessment

- Weight, height, BMI
- Estimated dry weight & BMI if ascites
- Weight history & estimation of % body weight loss (if applicable)
- Upper arm anthropometry (MUAC, TSF, MAMC)
- Hand grip strength

Dietary intake

- Current oral intake (establish if meeting energy & protein requirements)
- Eating pattern
- Influences on dietary intake i.e. any restrictions followed, social situation

Other

- DM control
- Renal function
- Vitamin status e.g. folate, vitamin B_{12}, vitamin D levels
- Bowel/malabsorption assessment

5.2.5 Allergy testing

Consider referral to the allergy clinic for patients with allergies likely to significantly complicate the transplantation process e.g. penicillin allergy.

5.2.6 Additional specific investigations

- Ascites – diagnostic ascitic tap including protein, albumin, glucose, TB and histology; obtain information regarding frequency of paracentesis.
- Pleural effusion – CT thorax; if diagnostic uncertainty, diagnostic tap
- Chronic encephalopathy – must have had brain imaging at some point since onset of symptoms (CT and/or MRI); if diagnostic doubt, measure arterial ammonia and consider EEG.

- Varices – ensure all patients with varices are receiving appropriate prophylaxis (see portal hypertension guideline); if not on prophylaxis ensure that all patients have had a screening OGD in the last 12-months (if not can be performed during assessment or in local hospital)
- Sarcopaenia – nutrition plays a crucial role in patients with chronic liver disease; all patients with advanced cirrhosis will have some degree of sarcopenia; all patients should be seen by the liver dietitian and have a formal baseline weight and body mass index, hand grip strength and upper arm anthropometry; nutritional supplements including in some cases NG feeding should be considered.
- Osteoporosis/osteomalacia – all patients with cirrhosis or cholestatic disease should receive oral calcium/vitamin D supplements (BSG guidelines 2002); assess fracture risk (https://www.shef.ac.uk/FRAX/tool.jsp) and request DEXA bone scan/treatment as recommended by the FRAX tool. In practice, nearly all patients attending for assessment for liver transplantation should have assessment with DEXA.

5.3 Radiology

- All patients: CT thorax and triple phase liver CT also covering pelvis
  - Note Doppler ultrasound liver no longer required routinely.
- DEXA if not already performed within 2 years
- CT thorax absolutely required if hepatocellular carcinoma or pleural effusion
- Hepatocellular carcinoma: at least two of triple phase liver CT, MRI, and biopsy; CT is required in all
- Primary sclerosing cholangitis: MRCP/MRI liver in the last 3 months; EUS/biopsy +/- ERCP/brushings ± cholangioscopy if dominant stricture/concern about cholangiocarcinoma
- Neck ultrasound/Doppler if re-transplant, or multiple previous neck lines/injections in order to check central vein patency
- Additional investigations will be guided by the transplant surgeon/radiology MDT meeting

5.4 Specific liver diseases/complications

5.4.1 Hepatopulmonary syndrome (HPS) – assessment and management:

Screening by oxygen saturations at assessment.
If O_2 saturations on air <96%, formal baseline ABG.
If confirmed hypoxia – lying and sitting ABG
Further investigation including contrast CT chest, microbubble echocardiogram and Technetium-MAA shunt study

HPS as the criterion for listing for liver transplantation:
According to UK selection criteria defined by LAG (https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/27372/pol195-120822.pdf) Section 3.2.1 under Variant Syndrome section

"Arterial pO_2 <7.8 kPa, alveolar arterial oxygen gradient >20 mmHg, calculated shunt fraction >8% (brain uptake following Tc^{99} macroaggregated albumin), pulmonary

vascular dilatation documented by positive contrast enhanced transthoracic echo, in the absence of overt chronic lung disease".

Liver transplantation contraindicated if:

Severe hepatopulmonary syndrome non-responsive to additional oxygen

5.4.2 Portopulmonary hypertension (PPH) – assessment and management

Screening by transthoracic echocardiography.

If suggested on echocardiography by raised tricuspid valve regurgitant velocity, with additional concerns → refer for right heart catheter study (with PVR measurement).

NB NHSBT Liver Selection Policy document. Also undertake CTPA.

Patients with portopulmonary hypertension (mean PAP >25 mmHg, <50 mmHg; PVR >120 dynes/s/cm^{-5}; PCWP <15 mmHg) should have had a clinically significant response to one of long-acting prostacyclin (or analogues), sildenafil, or bosentan."

Our current practice is that if MPAP >35 mmHg, refer to National Pulmonary Vascular Diseases Unit, Papworth

Liver transplantation contraindicated if:

- MPAP >50mmHg *OR*
- MPAP 35-50mmHg with PVR >250 dynes/s/cm^{-5}

5.4.3 Hepatocellular carcinoma

- See listing criteria for HCC (including potential downstaging)
- New HCC – discuss at HCC MDT regarding further staging and treatment options
- Treatment on Transplant Waiting List
- Consider for lesional therapy if possible pending transplantation
- Monitoring on Transplant Waiting List
- Repeat imaging and AFP at a maximum interval of 3 months and review at Liver Cancer MDT
- Decisions about removal or suspension from Transplant Waiting List to be made at Transplant MDT

5.4.4 Partial or complete portal vein thrombosis (PVT)

- Anticoagulation with therapeutic sc low molecular weight heparin unless contraindicated by significant thrombocytopaenia (decision at transplant MDT when listed). To be changed to full daily dose split in to two equal administrations 12 hours apart once listed.
- 3 monthly triple-phase CT to reassess PV/SV/SMV and review of CT to ensure remains transplantable
- Venous-phase CT when called in for a transplant to check remains transplantable

5.4.5 Primary sclerosing cholangitis (PSC)

- With known ulcerative colitis (UC):
  - Colonoscopy within the last 12 months with biopsies showing no malignancy
  - IBD needs to be under adequate control
  - For those in whom IBD is inadequately controlled, discussion with luminal gastroenterology regarding colectomy post-transplant is required.
- No known IBD:
  - Baseline colonoscopy.

5.4.6 Cystic fibrosis

- Assessment in liaison with Adult Cystic Fibrosis Unit, Papworth
- Particular attention to nutritional status and timing of lung vs liver vs combined
- Consistent route for pre-assessment evaluation re timing/order of organ transplantation – primarily via quarterly dedicated CF liver clinic (Dr Griffiths)

5.4.7 Hyperoxaluria

Plan timing of listing for transplantation – ideally prior to starting HD; liaison is required with the renal service.

5.4.8 Simultaneous liver-kidney (SLK) transplantation

Simultaneous liver and kidney transplantation is only undertaken when there is evidence of kidney failure that will not recover with a liver transplant alone.

The indications for SLK are:

- Genetic liver kidney syndromes, including hereditary oxalosis and Glycogen storage disease type 1

- Chronic liver disease meeting at least one of the three current criteria for liver transplant selection plus either:

  - end-stage renal disease on long-term dialysis
  - hepato-renal syndrome with serum creatinine >200 µmol/L and dialysis ≥6 weeks
  - GFR <30 ml/min (isotope or MDRD v6) or renal biopsy showing >30% fibrosis and/or glomerulosclerosis

All other cases should be referred to the National Appeals Panel.

Additional investigations/opinions

- Inform renal service in advance – typical main point of contact Dr N Torpey
- Check HLA status
- Formal nephrology opinion
- If prior haemodialysis, need imaging of central veins for patency

5.4.9 Acute on Chronic Liver Failure (ACLF)

A pilot of liver transplantation for patients with acute-on-chronic liver failure and poor prognosis recently completed and it is now possible to list for transplantation on this criterion.

Such patients should have cirrhotic chronic liver disease, be inpatients in a critical care unit, and have significant liver impairment with jaundice and coagulopathy. ACLF grade must be 2 or more.

Exclusion criteria, all relative, include age over 60 years, active bacterial or fungal sepsis, significant CMV viraemia, severe irreversible brain injury, overwhelming multi-organ failure, use of ECMO, active malignancy, severe acute pancreatitis, intestinal ischaemia. Uncontrolled alcohol use is also a contraindication.

Agreement is required from hepatologist, transplant surgeon, intensivist, and anaesthetist.

Patients listed under this scheme will be offered nationally allocated organs prior to offering for liver-intestine grafts in the organ offered schema.

5.5 Specific co-morbidities

5.5.1 Type 2 diabetes mellitus

- Optimisation of CVD risk factors
- Optimisation of DM control
- Assessment of CAD/LV function
- Assessment of DM end-organ damage

Factors that adversely affect long-term outcomes include:

- Neurovascular foot ulcers
- Peripheral vascular disease
- History of cardiovascular events
- Diabetic nephropathy
- Diabetic proliferative retinopathy

5.5.2 Patients with BMI >40

- Ideally referred for specialist weight reduction management before advanced liver disease
- Consideration of whether weight reduction is a pre-requisite for listing for liver transplantation.
- Referral for review by Tier 3 Obesity Service
- Consider for Cambridge Intensive Weight Management Programme (IWMP) pre-transplant
- Discussion about merits and timing of bariatric surgery in relation to transplantation – considered on a case-by-case basis

5.5.3 History of malignancy

Obtain history regarding original stage and treatment, as well as current prognosis (likely to need to involve the Oncologists especially if within the last 5-years)

5.5.4 History of known chronic kidney disease

Clarify previous history, obtain investigation results such as previous renal biopsy. See 'Renal investigations' section [5.2.2].

5.5.5 Alcohol/illicit drug use assessment

All patients with alcohol-related liver disease or a history of illicit drug use will be reviewed by a clinician/nurse specialist with expertise in addiction psychiatry and substance misuse.

Reports from the local alcohol support services and GP should be included in the assessment process.

A Psychiatric opinion may also be helpful in patients with a previous/current psychiatric illness or compliance issues.

5.5.6 Tuberculosis (TB)

Latent tuberculosis infection is the presence of Mycobacterium tuberculosis in the body without signs and symptoms, or radiographic or bacteriologic evidence of TB disease.

The interferon gamma release assay (IGRA e.g. Quantiferon®) may be superior to the tuberculin skin test in the immunocompromised, and in BCG recipients. It is specific but not fully sensitive; and does not differentiate between latent TB and TB disease. A positive result is diagnostic for latent or active TB. A negative result in a patient considered at high risk of latent TB should not be considered reassuring. The manufacturer suggests that up to 70% of patients who receive treatment for active TB may become Quantiferon® negative thereafter.

Patients undergoing liver transplant assessment should have a thorough assessment of risk factors for TB including travel history (see below). In patients with a past history of TB: collect information on diagnosis, site, sensitivities, and completeness of/compliance with treatment. All patients will have a CXR.

The following patients should have Quantiferon® testing during the transplant assessment:

- Patients born in, or who have spent a prolonged period of time in, high incidence areas (annual incidence rate >40 cases per 100,000 population).
- Close contact with a person with TB defined as prolonged and frequent contact e.g. household contact, frequent visitor to the house, boyfriend/girlfriend
- Patients with at least one of the following risk factors:

- History of homelessness
- Previous incarceration
- Hepatitis C, Hepatitis B, and/or HIV positive
- Alcohol excess
- Smoking history
- Ex-intravenous drug user
- Malnutrition
- Diabetes mellitus
- Previous solid organ transplant
- Previous haematological malignancy
- Previous gastrectomy
- End stage kidney disease
- Silicosis

In patients with a past history of TB: collect information on diagnosis, sensitivities, completeness of treatment; and seek specialist advice from the respiratory/ID teams.

Patients who have a positive Quantiferon® assay should be investigated for active TB:

- CT thorax (ideally compared to previous imaging by the cardiothoracic
- radiology team) and review of abdominal CT
- 3 x sputum, early morning urine and ascites for AAFB/culture

In patients with a past medical history of TB and/or a positive Quantiferon® result seek specialist advice from Dr Sian Stinchcombe, consultant respiratory physician.

In the absence of demonstrable active TB, the following patients should receive isoniazid 300 mg OD and pyridoxine 10 mg OD for 9 months post-transplant*:

- Quantiferon® assay positive *OR*
- Radiographic evidence of previous TB and no history of adequate treatment** *OR*
- Close and prolonged contact with a case of active TB *OR*
- Organ from a donor who was tuberculin skin test or Quantiferon® test positive, had recent exposure to active TB or had radiographic evidence of untreated TB

*In patients with impaired liver function, the risk benefit ratio probably favours deferring treatment until after transplantation.

**If a patient has had previous active or latent TB treated and current active or latent TB is felt to be unlikely then isoniazid/pyridoxine is not required.

All patients receiving isoniazid should have liver blood tests performed at 2 weekly intervals for 6 weeks (this is likely to be achieved by standard graft monitoring), then 1 monthly.

5.5.7 Schistosomiasis

Check schistosomal antibodies for all those from high prevalence areas (primarily sub-Saharan Africa) and treat with praziquantel 40mg/kg single dose as recommended by infectious diseases if positive.

5.5.8 Hepatitis A and Hepatitis B vaccination

The GP will be requested to vaccinate all Hepatitis A or B naïve patients for hepatitis A or B. Anti-HBs titres should be checked in previously vaccinated patients to ensure a booster is not required.

5.5.9 Strongyloides

Test for antibody positivity in those who have lived in areas where the disease is prevalent and if positive liaise with the infectious diseases team.

5.6 Liver transplant multi-disciplinary team (MDT) meeting

Weekly, except on Bank Holiday or day of Cambridge Liver Symposium.

Formal presentation of case by Hepatology SpR or SCF including all relevant information using standard transplant assessment proforma

The meeting is considered quorate if there is the following minimum attendance (in person or virtually):

- SpR/SCF who has met the patient and is able to present the case
- Liver transplant co-ordinator to represent views of assessing co-ordinator
- Minimum 2 consultant transplant surgeons
- Minimum 2 consultant hepatologists
- Minimum 1 consultant transplant anaesthetist

Referring gastroenterologist/hepatologist may be present virtually.

Conclusions:

Documented in MDT assessment in Epic

To be documented:

- Consultants present (in room and virtually)
- Options:
  - List
  - List pending further investigations (does not need to be re-discussion)
  - List pending further investigations (needs re-discussion)
  - Too early (deferred) and reasons for this
  - Declined listing for transplantation and reasons for this decision
- If listed, documentation of types of organ to be accepted (currently indicated as all patients being appropriate for DBD organs but with discretion as to DCD organs or split liver grafts)
- If listed, documentation for additional considerations at the point of admission for transplantation (imaging, laboratory, blood products etc.).
- Specific patient recommendations or requirements (e.g. stopping smoking, attendance arranged follow-up)
- Outstanding investigations or specialist referrals to be arranged.

- Specific monitoring on transplant waiting list (if listed)
- If listed for/with HCC, plan for on waiting list therapy for HCC and disease monitoring
- There may be specific requests for follow up imaging. Otherwise as per protocol (see under section 6).

Consider treatment dose low-molecular weight heparin if vessel thrombosis. Typically this is given in two equal doses twelve hours apart each day.

Immunosuppression may also be discussed at this time e.g. renal-sparing immunosuppression.

It is the responsibility of the Hepatology Registrar/Senior Clinical Fellow undertaking the assessment to complete the formal MDT document during the meeting including the outcome and plan. If the decision is deferred pending additional investigations, it is the responsibility of the assessing Consultant and recipient Transplant Co-ordinator to organise and complete the liver transplant assessments so that a final conclusion regarding liver transplantation can be made as soon as possible.

Communication from Liver Transplant MDT:

Liver transplant co-ordinator to call patients to let them know conclusions and plan.

Letter to patient and to referring consultant and GP by consultant hepatologist leading assessment.

Listing for liver transplantation

The letter from the consultant hepatologist to patients to be listed for liver transplantation will include the following information:

- reason for listing
- a re-stating of the mortality risk from liver transplantation
- the requirement for complete abstinence from alcohol in those patients in whom alcohol is felt to have contributed to their liver disease, together with the impact of alcohol being detected on the transplant waiting list (permanent removal) and the necessity to follow specific management to treat dependence as recommended by the transplant MDT in conjunction with liaison psychiatry
- in selected patients a contract of behaviour may be considered.
- necessity for avoidance of illicit drugs where there is a relevant history
- details of a request or requirement for smoking cessation

Confirmation of consent is to be obtained by a member of the surgical team at the time of transplant.

Active smokers will be advised to stop smoking; those with diagnosed end-organ damage relating to smoking or with diabetes will be required to stop smoking prior to listing as discussed above. Where appropriate, a letter will be sent to the GP requesting that they are referred to local smoking cessation services.

6 Transplant waiting-list management

All patients will be reviewed regularly in outpatients whilst awaiting transplantation. In most cases they will be seen in transplant waiting list clinic. If patients live closer to an outreach centre they may be seen primarily in the local transplant outreach clinic.

The focus of the outpatient consultations is to ensure the need and fitness for liver transplantation. This will take into account the following:

- UKELD and complications of portal hypertension
- Functional status
- Nutritional status – patients will be reviewed by the dietitian at least 3-monthly with repeat weight and body mass index, hand grip strength and upper arm anthropometry. Early intervention may be beneficial and NG feeding may be warranted in some cases.
- HCC status

Other issues to be addressed include donor options (e.g. higher-risk donors) and psychological difficulties.

Blood tests on the waiting list:

- FBC, U&Es, LFTs, INR at every visit
- CA19.9 every 3 months in PSC patients
- Check vitamin D level every 6 months and treat deficiency
- Viral screen does not need to be routinely performed whilst on the transplant waiting list unless required as part of monitoring chronic viral liver disease
- Additional bloods will be recommended by the consultant hepatologist
- If patients on the transplant waiting list have required a blood transfusion, two further samples will need to be taken for group & save to ensure no issues with blood transfusion when called in for transplant

Imaging on the waiting list:

- Cirrhosis – repeat ultrasound/Doppler every 3 months
- Hepatocellular carcinoma – MRI or CT every 3 months (unless dictated otherwise by the HCC MDT)
- Vessel thrombosis – triple phase liver CT every 3 months
- PSC – repeat MRI liver & MRCP if clinical change (should be done annually at a minimum)
- Ensure patient has had an assessment of bone density within previous 2 years
- Those with moderate aortic stenosis should have a repeat echocardiogram every 6 months

Reassessment criteria whilst on the transplant waiting list:

- Patients with hepatopulmonary syndrome should have a resting ABG at least every 3 months
- All listed patients will have a repeat mini-reassessment annually. The required tests will depend upon the specific recipient. This will involve an ECG and echocardiogram, ABG

if standing O_2 saturations <95%, with CXR and PFTs if specific concerns. In some cases the hepatology consultant will request a repeat anaesthetic opinion.

Specific treatments:

- Vessel thrombosis – treatment dose low-molecular weight heparin (dalteparin twice daily administration) in the absence of contra-indication
- Hepatitis C – most patients will be HCV RNA negative at the time of listing. If they are not then timing of treatment should be discussed at the liver transplant MDT
- Hepatitis B – antiviral therapy – patients should be HBV DNA negative going into liver transplantation by suppression with entecavir and/or tenofovir depending on the clinical context
- Alcohol related liver disease – active engagement with alcohol services; serum ethanol sent at every opportunity (including clinic visits/admissions for possible liver transplantation)
- Varices – standard prophylaxis, NSBB not contra-indicated in refractory ascites unless symptomatic hypotension, adverse effect or deteriorating renal function.
- Moderate-severe ascites +/- severe synthetic dysfunction – SBP prophylaxis regimen e.g. ciprofloxacin 250mg bd (or 500mg daily) or co-trimoxazole 480mg od.
- Severe synthetic dysfunction +/- biliary obstruction – may benefit from fungal prophylaxis (fluconazole 100mg od).
- Stop smoking – ensure referral to smoking cessation services
- At waiting list clinic patients may be approached to discuss research studies and/or clinical trials.

Co-ordination with transplant coordinator team:

- Consistent with the points details in the Transplant Coordinators Quality Manual including updating patient data on the national waiting list to ensure accurate representation for the Transplant Benefit Score.

Previously, it was required that all patients from the time of listing for liver transplantation, and long-term post-transplant as long as they are taking immunosuppressive agents, should receive hepatitis E negative blood components. All blood components in the UK are now screened as being hepatitis E negative.

7 Donor issues

All listed patients should have donor options considered and documented during the transplant MDT meeting (extended criteria DBD, machine DCD, split).

Patients offered on a place on the waiting list will have received information regarding the donor types and possible adverse effects. They will provide informed consent for specific higher risk organs.

Decisions regarding recipient-donor match when an organ becomes available will be made by the on call Hepatologist and Transplant Surgeon, and will take into account extended criteria status, location of donor, waiting list mortality, operative mortality, transplant benefit, issues in relation to perfusion and donor-recipient size.

7.1 Agreed protocol for DCD livers

Livers from DCD donors should undergo either normothermic regional perfusion in the donor, or *ex situ* machine perfusion.

Acceptable criteria for such donors are:

- Age under 70; donors over the age of 60 with type 2 DM are at higher risk of having MASH and should only be used after specific discussion about risks/benefits for recipient.
- Cardiac arrest within 3 hours of withdrawal of treatment
- No prolonged hypotension after treatment withdrawal (sBP <60 for >30 mins)
- Time from sBP < 50 mmHg until organ perfusion < 30 minutes.
- Asystole time (from cardiac arrest to cold perfusion < 20 minutes) unless using NRP
- Moderately-steatotic liver (on inspection at retrieval or on biopsy post retrieval) not recommended

Variations to be discussed between on-call consultant transplant surgeon/ hepatologist

Criteria for acceptance of DCD organs to be reviewed annually

7.2 Agreed protocol for HCV antibody positive donors

- This is addressed in a separate protocol available internally but the decision to proceed with an HCV positive donor requires agreement from patient, consultant hepatologist, and consultant transplant surgeon. Hepatitis C RNA PCR must be requested from donor and regularly from the recipient after transplantation. Critical care and transplant pharmacists should be pre-warned about the likely requirement for post-transplant treatment of HCV viraemia.

8 Admission for possible transplantation

Patients admitted for possible liver transplantation will be clerked in by the on-call transplant doctor (FY/IMT) and, if specific concerns, reviewed by the hepatology SpR on call to ensure that they are medically fit for surgery.

Time is of the essence, especially with the blood tests, as a different recipient may need to be sought. Blood samples are to be conveyed to the laboratory in person.

If there are any clinical concerns the hepatology SpR must highlight this to the hepatology consultant/transplant surgeon as soon as possible.

Their assessment will include the following:

Note: this is summarised in the Epic Order Set titled “Liver – Transplant Admission”, but please double-check requirements.

- History and examination
- Enquire about abstinence from alcohol
- Urgent FBC, U&E, LFT, Mg, coagulation screen, fibrinogen, ethanol level
- Urgent cross match for:
    - 10 units packed red cells
    - 1 adult dose of platelets (equivalent to 6 units).
    - 4 units of FFP for intra-operative use (thawed on request)
    - If the pre-op platelet count is <50 x 10^9/L a single adult dose (equivalent to 6 units) will be provided preoperatively and sufficient FFP to normalise the prothrombin time (please discuss administration timing with anaesthetist).
- Repeat virology screen if not sent in last 6 weeks (request OLT viral screen, which includes HBsAg, anti-HBsAb titre, HCV Ab, HIV, CMV IgG, toxoplasma IgG, HSV IgG, VZV IgG, EBV IgG)
- 10 mls blood for virology to store.
- 30 mls citrated blood **and** 10 mls serum – to go to tissue typing.
- Blood for current research
- ECG, CXR
- Diagnostic ascitic tap if symptoms to suggest SBP
- Urgent CT to evaluate portal vein thrombosis may be required (if required this will be specified on waiting list).

In addition:

- Repeat consent for operation by surgeon
- Urgent histology via on-call pathologist in liaison with recipient coordinator for lesions in donor liver, recipient, and/or for lymph node analysis.
- Donor viral status will be recorded by the transplant co-ordinator on EPIC

Contraindications to transplantation include:

- Recipient serum sodium <120 mmol/l; Na >120 but <125 mmol/l will be considered a relative contraindication and should be discussed with the transplant anaesthetist.
- If K >5.5 mmol/L on repeat testing consider pre-op CVVHD/dialysis

- Active infection other than intra-hepatic infection
- Active large volume bleeding
- Patient intoxicated – if concern about alcohol consumption – urgent blood ethanol and discuss with on-call consultant hepatologist.
- Any issues arising that give concern about appropriateness of proceeding with transplant to be fed back to on-call hepatology consultant urgently and/or consultant transplant surgeon

If transplantation does not proceed:

- Confirm whether discharge or continued admission is appropriate with the transplant surgeon on duty or hepatology consultant.

Remember to write up

- Intra-operative antibiotics – see perioperative antibacterial prophylaxis section below.
- Intra-operative immunosuppression 500mg methylprednisolone at end of anhepatic phase.
- For HBsAg positive recipient send 5000 units HBIg with patient (only stored in F5HDU drug fridge)
- If on warfarin, contact haematology to pre-request prothrombin complex concentrate to be sent to theatre with patient.

9 Immediate post-transplant management

On arrival in ICU post-transplant the hepatology registrar should review the patient and:

- Evaluate the indication for transplantation and co-morbidities
- Summarise relevant intra-operative surgical events (including arterial and biliary anastomoses), and donor details (including CMV, toxoplasma, EBV match status if known).
- Update problem list
- Summarise the current clinical picture including cardiovascular, respiratory and renal function, lactate and drain outputs.
- Inform the Hepatology Consultant of any clinical concerns without delay. Look out for increased lactate, high inotrope requirements, hypoglycaemia if not diabetic, bleeding. Patients may have a varying degree of ischaemia-reperfusion injury (increased prothrombin time and transaminases), but if ALT >1500 or INR >3.0 repeat bloods in 6 hours.

All patients should have:

- FBC, coagulation screen, fibrinogen, U&Es, LFTs, magnesium
- CXR to assess lines, exclude pneumothorax/effusion/consolidation
- Hourly ABG
- Request liver ultrasound/Doppler (to be performed within first 24 hours)

Clinical management will involve a partnership between hepatology, the surgeons and ICU:

- Most patients will require filling initially (may require 2-3 litres Hartmann's in first 12 hours). CVP is not a reliable indicator of intravascular filling status.
- Management of post-operative hypotension
- Ensure no signs of bleeding post-operatively
- Ensure adequately filled (patients warm to normal temperature post-theatre, hence may vasodilate)
- Traditionally inotropes were avoided in this setting because of a theoretical risk of reduced hepatic arterial blood flow and increased risk of thrombosis; however, maintaining the effective circulating volume (including via vasopressors) may be more relevant. On balance, "squeezing" should be avoided, but inotropes may be necessary aiming for a MAP of ~65 mmHg, especially in patients with post-operative SIRS. Swann readings/transoesophageal echocardiography should be encouraged in unstable patients.
- Maintain Hb at 70-80g/L.
- Platelet transfusion if <50 and active bleeding, or <15 (after checking with transplant team).
- FFP transfusion if INR >1.5 and active bleeding only
- Cryoprecipitate if fibrinogen <1g/L and active bleeding
- Patients may receive renal replacement therapy (RRT) intra-operatively.
- Once in ICU, the decision to commence CVVHD should involve both the Consultant Intensivist and the Consultant Hepatologist/Surgeon. Indications for RRT in this setting are graft failure (acute liver failure with encephalopathy/lactic acidosis) or acute kidney injury (uraemia, acidosis, hyperkalaemia, fluid overload).

- Intravenous n-acetylcysteine (150mg/kg in 100ml 5% glucose infused centrally over 24 hours i.e. 6.25ml/hour) may be recommended by the transplant surgeon or hepatologist in the setting of significant graft injury.

The hepatology registrar is expected to prescribe the initial prophylaxis and immunosuppression:

- Pantoprazole 40mg IV od
- Antibiotic prophylaxis (see below)
- Antifungal prophylaxis (see below)
- TB prophylaxis if indicated (see below)
- Valganciclovir prophylaxis if CMV mismatch (see below)
- Co-trimoxazole as PJP prophylaxis with modification (see below)

Immunosuppression (see also section 13):

- Prednisolone 20mg od to start day 1 post-transplant
- Azathioprine or mycophenolate (MMF) to be introduced following review by the hepatology consultant
- Calcineurin inhibitor (CNI) therapy will normally be prescribed following review by the hepatology consultant
- If acute kidney injury, CNI may not be used in the first few days and alternatively basiliximab (IL-2Rα) antibody will be prescribed following review by the hepatology consultant

All preoperative medication for decompensated chronic liver disease other than anti-viral treatment should be discontinued. Oral anti-hepatitis C & B treatment MUST be continued. Hepatitic C treatments funded on an individual patient basis due to expense, as such stock is not held for all the different genotype regimens- recipient must be advised to bring home supply with them. Anti-hypertensives and statins should be withheld in the short-term.

In patients on long term oral opioids including methadone, their baseline medications should be started early after transplantation (see analgesia section below).

Start parenteral nutrition early if unable to take oral intake (the nutrition team will advise regarding PN regimen).

10 Post-transplant management on ICU

10.1 ICU admission paperwork

ICU clerking

- Indication for transplant, commenting on features of decompensation particularly pre-operative ascites (expect higher drain output), encephalopathy (may take longer to extubate)
- Co-morbidities and baseline functional status
- Intra-operative events: Anaesthetic – volume of blood and products transfused, response to reperfusion, use of intra-operative CVVHDF, use of bypass; Surgical – details of anastomoses and reconstructions (e.g. biliary reconstruction – duct to duct or Roux limb, venous jump grafts), any abnormal vascular anatomy, estimated blood loss, need for veno-veno bypass, plans to return to theatre (e.g. if liver is packed), drains
- Organ specific: DBD/ DCD (graft may be slower to function), split graft, condition of organ implanted e.g. fatty liver, normothermic regional perfusion/OrganOx® time
- Summarise the current clinical picture including cardiovascular, respiratory, renal function and support, lactate, and drain outputs

10.2 ICU investigations

- Bloods: FBC, U&Es, LFTs, Ca, Mg, PO4, coagulation profile including fibrinogen. TEG may be considered if ongoing bleeding and clinical need to replace blood products
- ABG
- CXR to assess line position, exclude pneumothorax/ effusion/ consolidation
- Drain bilirubin at day 3 (timing of drain removal will be reviewed daily by transplant surgical team)
- Ultrasound liver Doppler to assess vessel patency and flow and biliary dilatation (to be performed within first 24-36h)

Order sets on Epic

- Standard ICU admission order set including MRSA decolonisation and mouth care
- Pharmacological VTE prophylaxis is on advice from surgeons – a VTE assessment must be done
- Antibiotics and antifungals (see section 12)

10.3 ICU immediate management

- Early extubation (within 4h of ICU admission):
  - A proportion of patients will be suitable for an early extubation pathway based on their intra-operative trajectory and physiology both in theatre and post-operatively on ICU
  - The anaesthetist will handover if a patient is suitable for early extubation, potentially suitable for early extubation following a period of optimisation, or unsuitable for early extubation

  - If the patient is suitable (or potentially suitable) for early extubation then the ICU early extubation guidance flowsheet should be followed to optimise the patient and reach a point where the patient is ready to be extubated following ICU consultant review
- If a patient is unsuitable for early extubation they should be resuscitated and stabilised and kept sedated and ventilated

See appendices 0 & 32 for early extubation flowsheets

10.4 ICU weaning sedation and ventilation

- Post liver transplant patients are admitted to the ICU for a period of postoperative ventilation and/or fluid management
- Mandatory ventilation using lung protective parameters is usually initially required (usually PRVC)
- Aim to transition to PS/CPAP when haemodynamically stable, anticipating extubation
- In situations where a return to theatre is planned, patients should remain intubated and ventilated
- Sedation is usually maintained with propofol and remifentanil or fentanyl and should be weaned to allow patients to transition to PS/CPAP, maintain tube tolerance, and patient comfort

10.5 ICU fluid management

- Initial post-op fluid requirements post-op are generally high because of fluid shifts/vasodilatation, resulting in a significant amount of catch-up on ICU
- Hypotension due to hypovolaemia may be treated with Plasmalyte® and 4.5% HAS depending on albumin (<25g/L) and drain output
- If drain output is high due to ascitic losses replace with HAS as per ascites protocol (100mls 20% HAS for every 3L ascites drained)
- Caution is required with the use of fluids with a supranormal concentration of chloride ions, such as 0.9% normal saline, Gelofusin®, and 4.5% HAS. These can worsen base deficit by increasing serum chloride concentration, leading to a hyperchloraemic metabolic acidosis
- Although coagulation may be deranged, blood products should not be given unless there are signs of significant bleeding or specified by the transplant surgeon due to the operative field. Calcium may be low because of citrated blood products and ionised calcium (iCa) should be kept > 1.1 mmol/L
- Vasopressors may be required to maintain sympathetic tone in the context of sedation and vasoplegia. However, they should be used judiciously due to the risk of reducing hepatic arterial flow and compromising liver blood flow, and should be started only with senior ICU input. A MAP of 60 mmHg is appropriate for most patients.
- Urgent senior ICU +/- surgical review may be required if pressor requirements are high (noradrenaline >0.2mcg/kg/min) and continuing to escalate, or if lactate remains high or starts to increase
- Fluid therapy should be titrated to static and dynamic measures of volume status
- Static measures include heart rate, blood pressure, urine output, capillary refill time, and lactate. These are helpful when assessed as a trend but are insensitive to predicting fluid responsiveness

- CVP is a static marker of volume status and does not accurately reflect left ventricular preload nor fluid responsiveness. While its trend may be useful, it should not be relied upon as a single measure to guide fluid resuscitation. However, a very low CVP (< 6 mmHg) or a falling CVP may indicate hypovolaemia or ongoing fluid losses.
- Dynamic markers (measures vary with changes to preload) include passive straight leg raise, stroke volume variation (SVV) and pulse pressure variation (PPV), which can be derived from the arterial line trace; a PPV >10% in a patient on mandatory ventilation and in sinus rhythm suggests fluid responsiveness
- CO monitoring (PiCCO, LiDCO, PAFC) should be considered for haemodynamically unstable patients and can help guide fluids and vasopressors/ inotropes
- A bedside transthoracic echocardiogram may help determine the need for fluid/ionotropes/pressors

10.6 ICU management of acid-base balance

- Metabolic acidosis is frequently seen and requires treatment of the cause prior to extubation
- If a raised base deficit is secondary to tissue hypoperfusion, restoring circulatory volume should correct the abnormality
- The intra-operative of potassium sparing fluids (Gelofusin® and 0.9% normal saline) can contribute to a hyperchloraemic metabolic acidosis
- If the base excess is persistently less than -5 despite adequate filling and a falling lactate start 8.4% $NaHCO_3$ at 25ml/h via central access, aiming to stop when base excess is greater than -2 or sodium > 150 mmol/L, whichever comes first (take care to avoid rapid rises in Na concentration)
- Similarly, while a raised lactate may represent a state of reduced perfusion, its aetiology may include a failing liver, sepsis, and use of inotropes such as adrenaline. A persistently raised or rising lactate must be escalated to seniors including the hepatology and transplant surgical team immediately and an urgent US or CT triple phase should be considered

10.7 ICU renal support

- Some patients may require continuous renal replacement therapy (CRRT) intra- and/ or post-operatively
- Indications to continue CRRT post-operatively include graft failure (acute liver failure with encephalopathy/ lactic acidosis/ electrolyte derangements), acute kidney injury (pre-existing, and/or secondary to intra-operative stress of transplantation – hypotension, resuscitation, fluid shifts) – which may be worsened by contrast loads associated with repeat imaging
- It is notable that many patients demonstrate oligo-anuria and a degree of acidosis in the first 72 hours and do not require renal support
- Renal support should not be started without discussion with an ICU consultant
- Bypass lines cannot be used for renal replacement therapy and a vascath will have to be inserted.

10.8 ICU coagulopathy

- Do NOT correct coagulopathy (PT, APTT, platelets) without discussion with the transplant surgeon/ hepatologist/ ICU consultant
- Coagulopathy is generally only corrected in the context of active bleeding due to risk of causing thrombosis in the new vessels supplying the graft leading to graft loss
- Maintain Hb >70g/L.

10.9 ICU imaging

- US liver with Dopplers is routine in the first instance and needs to be undertaken within the first 24-36h (but should not delay extubation)
- If there are concerns regarding the vasculature, or it is not well visualised a CT triple phase may be indicated after discussion with the transplant surgeons and hepatologists
- Further management may involve repeat US liver with Dopplers or CT after a period of time, or a return to theatre

10.10 ICU analgesia

- A morphine/ oxycodone/ fentanyl (if renal impairment) PCA is usual. Patients should be given a loading bolus prior to extubation
- Paracetamol is usually not used but may be given after discussion with the duty consultant.
- Regional anaesthetic techniques are not generally used for liver transplants because of concerns with bleeding and coagulopathy

10.11 ICU dysnatraemia

- Hyponatraemia is seen in approximately 20% of patients with end-stage liver disease and is defined as a sodium ≤130mEq/L. Hypernatraemia is seen less commonly and refers to a sodium >145mEq/L
- Management of hyponatraemia is challenging and depends on volume status and the underlying cause
- Overcorrection of sodium can lead to osmotic demyelination syndrome which can be fatal
- The goal of sodium correction in these patients is ≤ 4-6mEq/L over a 24h period. Fluids with a low concentration of sodium (e.g. 20% HAS, 0.45% NaCl) should be used and patients may require renal replacement therapy with diluted filter bags to control sodium. Early discussion with ICU consultants is required.
- If blood product transfusion is indicated, discuss with haematology as prothrombin complex concentrate or fibrinogen concentrate may be required instead of FFP and cryoprecipitate respectively, as these do not contain a sodium load

11 Subsequent post-transplant management

11.1 Line/drain care

Daily check of insertion skin site and skin dressing/ coverings

Bypass lines not to be used for infusions/injections/renal support on HDU

Bypass lines to be removed prior to leaving ICU

Swann sheath to be removed within 24hrs of transplant (unless clinically still required).

Requirement for arterial line and central line to be reviewed on a daily basis and removed as soon as possible. If renal function reasonable and no concerns re fluid status, remove central line. If IV access needed for drugs/PCAs etc, patients may benefit from a PICC line.

Timing of drain removal to be supervised by transplant surgical team. Drain fluid to be examined daily and sent for fluid bilirubin if suspicion of bile leak and routinely on day 3.

Adherence to the Trust's management of risks associated with infection prevention and control (IPC) strategy is of paramount importance.

11.2 Nutrition

Feeding is usually started following extubation. Defer if the patient has a Roux limb unless the Roux limb pre-dates this transplant.

Usually the patient begins with sips, progressing to free fluids, a soft diet, and a normal intake. Post-transplant patients have particularly high requirements for energy and protein. They tend to be prescribed liquid oral supplements once they can have free fluids, which may be continued when normal eating is established.

If patients are not extubated early or unable to meet their requirements orally then there should be a low threshold for recommending enteral feeding, usually via an NGT. NJ tubes can be inserted endoscopically if required. If enteral feeding is not tolerated then PN is recommended. Use low volume/ high concentrate PN if necessary due to volume status.

Enteral tube feeding (or PN) should be continued until adequate oral intake is being maintained. Record charts should be kept to monitor nutritional intake wherever possible patients should be on a high protein/ high energy diet, unless any other dietary restriction is needed to be imposed. The dietitian will advise on this.

Patients are given food safety advice before discharge from hospital and recommended to follow this until they are on a maintenance dose of immunosuppression. Following this they are advised to follow normal food safety precautions.

The patient should continue on the high protein/ high energy diet until weight is within an ideal range for height. Healthy eating should then be encouraged. Patients who become overweight should be re-referred to the dietitian for advice. Patients are reviewed by the dietitian in the post-transplant clinic for a duration dependent on their nutritional status.

11.3 Analgesia

All liver transplant recipients on return to HDU/ward will be offered a PCA provided there is no contraindication. In most cases the PCA will be prescribed by the ICU team; and continued after transfer to F5 for ~24-48 hours.

Postoperative PCA prescription

50 mg morphine sulphate to 50 mls 0.9% saline.

Loading dose:	*Nil*
Bolus:	*1 ml*
Dose duration:	*stat*
Lock out period:	*10 minutes (altered if necessary – minimum lock out period 5 minutes)*
Concentration:	*1 mg/ml*
Background:	*Nil*

Analgesia for Methadone users (Weinrieb et al Liver Transplantation 2004; 10; 97-106)

- Start an early explanation of analgesic route and rationale prior to OLT; record methadone usage on waiting list record and inform ward of prior methadone usage. Explain further addiction problems will not occur via PCA opiate usage.
- Immediately after surgery restart methadone at usual daily dose divided 12 hourly via nasogastric tube.
- Basal rate will be approximately morphine 3-5 mg/hour with 2-5 mg morphine every 10-15 minutes on demand.
- Symptoms of opiate withdrawal may occur without any pain; note pupillary size, agitation, sweating, rhinorrhoea, yawning.
- When weaning off PCA patient may need an increase in methadone of up to 50% from pre-OLT dose.
- There are no known drug interactions between methadone and prednisolone, azathioprine, ciclosporin, tacrolimus, MMF, nystatin, co-trimoxazole.

11.4 Routine investigations

FBC	**daily**
U&E	**daily**
CRP	**daily**
LFT	**daily**
PT	**daily**
Doppler ultrasound	Within first 24 hours post-transplant, and weekly prior to discharge. Specifically request visualisation of arterial inflow at the porta hepatis and in both lobes of the liver (can have branch hepatic artery thrombosis). High-resistance waveforms are not always pathological.
Tacrolimus, ciclosporin and/or sirolimus levels.	**Daily trough/pre-dose level (NB no assays on Sundays).** All inpatients should have level sent daily in an EDTA bottle. This needs to be in the lab by 10AM.
Viral screen	Monday on all liver transplant patients including CMV/EBV/Adenovirus PCR plus HCV RNA, anti-HBsAb titre, HBV DNA if appropriate
$Mg^{2+}/PO_4^{2-}/Ca^{2+}$	Minimum of twice weekly on all transplant patients

An Order Set on Epic entitled ‘Liver - Transplant Post Op’ facilitates placing orders appropriate for most post-transplant liver patients.

12 Peri-transplant prophylaxis

12.1 Peptic ulcer prophylaxis

- Pantoprazole 40mg IV od changed to oral PPI (standardly omeprazole 20mg od) on discharge from ICU. Peptic ulcer prophylaxis should be continued as long as the patient is on prednisolone.

12.2 Thrombosis prophylaxis

- Dalteparin prophylactic dose from day 1 post-transplant unless concerns regarding bleeding risk (clarify with transplant surgeon).
- Aspirin 75mg od from day 3 unless concerns regarding bleeding risk (clarify with transplant surgeon).
- **All patients will be discharged on aspirin unless contraindicated**. In patients with a significant past history of peptic ulcer disease co-prescribe a proton pump inhibitor long-term.
- Higher risk recipients will receive long-term formal anti-coagulation: treatment dose dalteparin initially converted to oral anti-coagulation after 3 months (see 'Anti-thrombotic treatment' below for more detail). Risk status will be determined by the Surgeon and Hepatologist and will take into account pre/peri-transplant vessel thrombosis, anatomy, recipient procoagulant state.

12.3 Antibacterial prophylaxis

Routine:

- Piperacillin-tazobactam 4.5g with pre-medication, during haemostatic pause (after completion of PV and HA anastomoses) and 8 hourly for 48 hours (adjusted for renal function)
- If patient known to be ESBL carrier, use meropenem 1g 8-hourly instead
- If patient known to be MRSA +ve, add vancomycin 15mg/kg 12-hourly and adjust for renal function.
- If the recipient or donor is known to be colonised with VRE, CPE or other multiresistant Gram negative organism, discuss appropriate prophylaxis with Microbiology.
- Continue routine prophylaxis for 48 hours with the caveat below

NB If concern re, or demonstration of, donor sepsis, antibiotic prophylaxis to prevent transfer of sepsis should be dictated by donor results/cultures – discuss with Microbiology.

Penicillin-allergic patients irrespective of MRSA status: Ciprofloxacin 400mg IV bd plus metronidazole 500 mg IV tds plus vancomycin all with pre-medication continued for 48 hours. Vancomycin dosage depends on renal function, please refer to trust guidelines (http://connect/utilities/action/act_download.cfm?mediaid=20827).

Patients with hepatic infarction, acute liver failure, or re-transplant during the current admission: give prophylaxis as above for antibacterials and for a high-risk recipient in relation to anti-fungal prophylaxis. If they remain on ICU do not stop antibiotics without discussion with consultant hepatologist, intensivist and microbiologist.

NB Continue antibiotics for minimum five days if febrile post-op, CRP not settling, early evidence of septic focus e.g. wound (consultant on duty to advise), or falling into the groups in the paragraph above.

12.4 Fungal prophylaxis

High risk patients:

For high-risk patients suggest anidulafungin 200mg stat then 100mg od or caspofungin 70mg od loading, then 50mg od if <80kg otherwise continue with 70mg od. Caspofungin is ideally avoided in the setting of graft failure otherwise a dose reduction may be indicated.

Patients are considered high risk if they have

- One of the following:
    - Transplanted for acute liver failure
    - Re-graft
    - On renal replacement therapy
    - Super-urgently listed for re-transplantation

- Or two or more of the following:
    - Intra- or peri-operative transfusion of ≥20 units of cellular blood products (red cells/platelets)
    - Need for choledochojejunostomy
    - Two or more positive clinical site surveillance cultures (nasal, pharyngeal, or rectal) for Candida from 48 hours before to 48 hours after LT
    - Repeat abdominal surgery within 7 days of liver transplant

- In some cases patients may benefit from a prolonged course of antifungal prophylaxis:
    - acute liver failure with renal failure
    - re-transplantation
    - concerns about an ischaemic graft
    - high dose immunosuppression
    - biliary complications

Low risk patients:

Start with IV and switch to PO (when extubated or absorbing from NG) fluconazole 100 mg daily. Nystatin should continue until the prednisolone dose is below 10 mg per day – Calcineurin Inhibitor levels may drop on stopping fluconazole. See interaction section for further detail.

Fluconazole dosage in renal impairment:

As per separate guideline (see Merlin)

- CrCl (ml/min) 10-50: Normal dose
- CrCl (ml/min) <10: 50% of usual dose
- Haemodialysis: Single dose unit (100 mg) after each dialysis session

- Haemodiafiltration (CVVHDF): prophylactic dose 200 mg daily, treatment dose 800mg daily (significantly cleared by CVVHDF therefore usual dose is doubled).

Fluconazole has good oral bioavailability (~90%) so oral therapy should be used where possible.

Consider stopping fluconazole at the point of stabilisation (functioning graft and therapeutic CNI level) and return to the transplant ward.

12.5 CMV prophylaxis

Donor virology sample is sent to CUH lab for confirmatory testing and the transplant coordinators will check this repeat result and alert the clinical team should there be any discrepancy.

Donor+/Recipient- (D+/R-) ('CMV mismatch')

D+/R- are at risk of de novo infection and will be receive Valganciclovir prophylaxis from immediately post-transplant to 3 months. Valganciclovir dose varies according to creatinine clearance (see table). CMV PCR should be sent weekly until hospital discharge and then at every clinic appointment until 12 months post-transplant.

Creatinine clearance (ml/min)	Prophylactic dose
≥ 60	900mg od
40–59	450mg od
25–39	450mg every other day
10–24	450mg twice weekly
< 10	450mg once a week

D+/R+ and D-/R+

Patients with D+/R+ and D-/R+ are at risk of CMV reactivation. These patients should have weekly CMV PCR during hospitalisation and then at every attendance at clinic until 6 months post-transplant.

D-/R-

D-/R- do not require screening and should only have a CMV PCR sent if clinical suspicion of CMV disease (e.g. unexplained pyrexia, transaminitis, leucopaenia, diarrhoea). See under 'CMV infection' section.

Note – Donor CMV IgG negativity MUST be confirmed by CUH testing – there have previously been instances where local and NHSBT provided testing has been discordant.

Retransplantation

Individuals receiving a second or subsequent liver transplant should be managed according to the same principles as for first transplant recipients above. Specifically, if the recipient is seronegative and either the current or a previous graft is seropositive, then prophylaxis should be considered.

12.6 Pneumocystis prophylaxis

PJP prophylaxis should be given to the following patient groups:

- All liver transplant recipients during the first 3 months post-transplant
- Patients receiving ATG or alemtuzumab (Campath®)
- Patients with lymphopaenia receiving high dose immunosuppression at any time post-transplant

First line PJP prophylaxis is co-trimoxazole 480mg 3 times weekly (Mon, Wed, Fri).

Consider dapsone 100 mg daily if co-trimoxazole sensitivity. **Note: dapsone is not suitable if the patient has a sulfonamide/sulfone allergy as co-trimoxazole and dapsone both contain a sulfa moiety. Test for G6PD deficiency before initiation.**

Anaphylaxis has only been reported very rarely to sulfonamides, however hypersensitivity reactions that may be caused by sulfonamides include:

- fever
- skin reactions (including Stevens-Johnson syndrome)
- Systemic lupus erythematosus
- nephrotoxic reactions
- blood disorders
- syndrome resembling serum sickness
- hepatic necrosis
- hepatomegaly and jaundice
- myocarditis
- pulmonary eosinophilia
- fibrosing alveolitis.

Alternative toxoplasma prophylaxis needed if co-trimoxazole is not tolerated - see section below.

12.7 Toxoplasma prophylaxis

If donor positive and recipient negative start oral co-trimoxazole 480 mg daily or pyrimethamine 25 mg od for 6 weeks (combine pyrimethamine with oral folinic acid 15 mg od to prevent sequelae of folate antagonism with pyrimethamine). Where donor status is unknown, assume positive and give prophylaxis.

Change to co-trimoxazole 480mg three times per week after initial 6 weeks for a further 6 weeks for PJP prophylaxis (3 months total).

12.8 Anti-tuberculous chemoprophylaxis

For patients with CXR changes and/or past history of TB and/or positive TB Quantiferon® assay:

The internationally recommended prophylaxis is isoniazid 300 mg/day for 9 months with pyridoxine 10mg daily.

Also see above

12.9 Donor antibacterial prophylaxis

Donor pre-hepatectomy: Piperacillin-tazobactam 4.5g IV; if ESBL colonised, use Meropenem IV instead; if known MRSA positive, add vancomycin IV.*
Perfusate: Ampicillin 1 gram plus gentamicin 8 mg per litre.
*If the recipient or donor is known to be colonised with VRE, CPE or other multiresistant Gram negatives organism, discuss appropriate prophylaxis with microbiology.

Usually can use a donor who has had sepsis prior to donation if had antibiotics for more than 48 hours. Discuss donor prophylaxis with microbiologists first and possible change to recipient prophylaxis for more than usual 48 hours. The microbiologists do a round on Friday morning when patients may be discussed.

13 Immunosuppression

13.1 Intra-operative

Methylprednisolone sodium succinate 500 mg at end of anhepatic phase.

13.2 Days 1 to 7

Immunosuppression is the responsibility of the liver transplant team including when the patient is in ICU.

Immunosuppression regimens are increasingly being tailored to the individual. The goal is prevention of rejection with the least possible immunosuppression, to minimise long-term extra-hepatic complications. Patients who are higher risk of rejection, or of extra-hepatic complications of the calcineurin inhibitor (CNI), can be identified at the time of transplantation. Therefore, the Consultant hepatologist and transplant surgeon will frequently prescribe a modified regimen at this stage.

The standard immunosuppression protocol is:

Prednisolone:

20 mg/day NG/oral from day 1

In patients with prolonged portal vein clamping and secondary bowel oedema there is a theoretical concern of reduced steroid absorption and iv hydrocortisone 100mg bd can be considered as an alternative.

Azathioprine (or mycophenolate mofetil):

1 mg/kg/day NG/oral from day 1 rounded to nearest 25mg.

The alternative is mycophenolate mofetil (MMF) 500mg-1g bd (maximum dose 1.5g bd) in patients at increased risk of rejection, receiving renal sparing immunosuppression, or with previous adverse effects of azathioprine, or if treatment of hyperuricaemia with allopurinol or febuxostat.

Mycophenolate mofetil exposure in the first trimester is associated with a high rate of foetal malformation. It is recommended that it is used with caution in females of child-bearing age, who should be informed of the risks and should be advised to use two reliable forms of contraception simultaneously during therapy and for six weeks after discontinuation. Sexually active men should use condoms during treatment and for 90 days after cessation of treatment; and their female partners should use highly effective contraception for the same time frame. See appendix 4.

Tacrolimus (Adoport®):

Starting dose 2-4mg bd aiming for a trough level of 5–8 µg/L

Dose is prescribed without an end-date, reviewed daily and adjusted if needed according to the trough level and side-effects (renal function, neuro-psychiatric state).

In patients at increased risk of rejection (such as patients transplanted for primary sclerosing cholangitis, autoimmune hepatitis or primary biliary cholangitis, recipients with previous rejection, or re-transplantation for chronic rejection) higher trough levels may be indicated (8–12 µg/L).

In patients receiving renal sparing immunosuppression aim for a trough of 5–7 µg/L; and in some cases the tacrolimus will be omitted until day 5 (see 'Renal sparing immunosuppression' below).

Patients with a low serum albumin have higher levels of free tacrolimus initially until steady state is released and so may be more prone to its side effects (neuro-psychiatric and renal). The assay measures the total amount of tacrolimus in the blood.

Patients with initial severe liver injury/graft failure usually require less immunosuppression and are at high risk of sepsis and acute kidney injury. Therefore, in these patients the CNI may be withheld until clinical improvement.

Tacrolimus Levels:

Blood for tacrolimus/FK assay should be trough/pre-dose samples only. One separate red EDTA tube needed. The assays are performed every Monday to Saturday (not available on Sunday). Samples *must* be in biochemistry laboratory before 10:00 hours otherwise need to phone as special request (which is usually turned down, especially on a weekend).

NB: **Advagraf®** is being dispensed on the ward to renal transplant patients but is a long-acting tacrolimus, prescribe by brand in Epic.

NB: Some older transplant patients will be maintained on the Prograf® brand of standard release tacrolimus. If patients are re-transplanted they should switch to Adoport post transplant. A switch can be under-taken outside of a re-transplant to Adoport (same daily dose), as long as a repeat tacrolimus level is checked 1-2 weeks post switch to check the level is still within target range for the patient.

13.3 Day 7 onwards

The main cause of long-term extra-hepatic complications is the CNI; therefore, tacrolimus/ciclosporin exposure should be kept to the minimum dose possible.

The choice of immunosuppression regimen should be documented in the Epic problem list (i.e. standard immunosuppression with azathioprine; renal sparing immunosuppression with MMF) including target tacrolimus trough levels

Prednisolone:

Reducing dose from 7-14 days post-transplant and continued until 6-12 weeks in all patients except those on long-term steroids pre-transplant, or recipients with recurrent or late-onset acute cellular rejection.

Azathioprine or mycophenolate mofetil:

Most patients benefit from a second agent long-term post-transplant. Azathioprine/Mycophenolate should be continued in patients at high risk of rejection (indication for transplant autoimmune liver disease including PSC and PBC, already treated for rejection/chronic rejection, regraft for chronic rejection) and in patients at risk of the extra-hepatic complications of CNI (especially risk of CKD, diabetes). See 'Renal sparing immunosuppression' section. Azathioprine/mycophenolate should be stopped if possible in patients who develop malignancy.

If neutropenia develops either reduce the dose (i.e. if count $<2 \times 10^9$/L), or stop if more severe/progressive, or infected. Temporary suspension with reintroduction ~2 weeks later at a lower dose may be appropriate. If otherwise unexplained macrocytic anaemia reduce dose.

Ideally avoid co-administering azathioprine and allopurinol or febuxostat unless essential and the significant interaction is managed by reducing the azathioprine dose by 75% with careful monitoring.

Tacrolimus (Adoport®):

Patients should be maintained long term on the lowest possible dose to prevent graft rejection. Long term trough levels should be individualised. In many patients this will be a trough level of 5–7 µg/L initially, adjusting according to renal function. In patients at increased risk of rejection (such as patients transplanted for primary sclerosing cholangitis, autoimmune hepatitis or primary biliary cholangitis, previous acute rejection, re-transplantation for chronic rejection) higher trough levels may be indicated (8-12 µg/L). Many older patients transplanted for non-immune-mediated liver disease will tolerate trough levels of ~3µg/L from 6-12 months post-transplant. In a renal sparing immunosuppression regimen the trough should be <5µg/L, and potentially ~3µg/L from 6-12 months post-transplant (see 'Renal sparing immunosuppression' below).

Secondary hyperkalaemia may respond to oral sodium bicarbonate (500mg to 1g qds).

Ciclosporin (Neoral®):

Reserved for patients with adverse effects to tacrolimus (e.g. neurotoxicity).

Usual starting dose is 100mg bd aiming for a trough of 100-150 µg/L in the peri-transplant phase; long term many patients have adequate immunosuppression with a trough of 50 µg/L.

Sirolimus:

May be used for renal sparing immunosuppression (see 'Renal sparing immunosuppression' below), but not normally within the first 12 months of transplantation (it is vital not to stop the CNI prematurely).

Start at 2 mg/day and continue the CNI for at least 2 weeks at half dose until stable with a sirolimus trough level of >4µg/L. If develop side-effects on sirolimus, reduce the dose but do not stop the CNI until on a stable regimen.

Important side effects to remember are proteinuria and impaired wound healing. When major elective surgery is planned, sirolimus should be considered for switching to an alternative immunosuppression regimen for at least 10-14 days beforehand because of the long half-life, and not restarted for 1-3 months afterwards.

13.4 Renal sparing immunosuppression

Renal dysfunction following liver transplantation is frequently irreversible; therefore, prevention of chronic kidney disease should be a key focus of care. CNI minimisation from early post-transplant is associated with less renal loss. The purpose of renal sparing immunosuppression is to expose patients to the lowest dose possible to protect graft function, prevent rejection and to minimise renal injury. In higher risk patients with a lower risk of rejection, formal renal sparing immunosuppression may be initiated.

13.4.1 Peri-transplant

At the time of transplantation renal sparing immunosuppression should be considered in the following patients:

- Pre-transplant intrinsic chronic kidney disease with MDRDv6 eGFR<60 ml/min
- Pre-transplant refractory ascites
- Peri-transplant acute kidney injury (creatinine rise >2 × baseline)

Older recipients, females, patients with type 2 diabetes mellitus, and the obese are at increased risk of chronic kidney disease. If multiple risk factors, renal sparing immunosuppression may be appropriate.

Patients at high risk of rejection should not receive a renal sparing immunosuppressive regimen.

The two current renal sparing immunosuppression regimens initiated at time of transplantation are delayed introduction of CNI with IL-2 receptor alpha subunit antibody

cover (basiliximab), or low dose CNI from day 1 with mycophenolate mofetil. There is no convincing evidence currently that delayed introduction offers additional advantage over low dose. There is a theoretical advantage, but cost implications. Therefore the decision will be made on an individual case basis.

Renal sparing with delayed CNI: basiliximab 20mg IV on day 1 and 4, Mycophenolate Mofetil (500mg-1g bd) from day 1, low dose tacrolimus from day 5 aiming for a trough of <5µg/L, standard reducing dose of prednisolone.

Renal sparing with low dose CNI: low dose tacrolimus from day 1 aiming for a trough of <5 µg/L, mycophenolate mofetil (500mg-1g bd) from day 1, standard reducing dose of prednisolone.

After discharge patients should remain on mycophenolate mofetil long-term and the lowest possible dose of tacrolimus (trough level <5 µg/L), potentially ~3 µg/L from 6-12 months post-transplant. If patients are intolerant of mycophenolate they should be switched to azathioprine.

13.4.2 In patients with chronic kidney disease

In patients receiving standard immunosuppression who develop chronic kidney disease, renal sparing immunosuppression should be considered. The regimen choice will take into account time post-transplant, risk of rejection and co-morbidities. Renal sparing should be commenced sooner rather than later; renal dysfunction in this setting is rarely reversible.

The renal sparing immunosuppression regimens that may be helpful at this stage are reduced dose CNI with mycophenolate mofetil; or replacement of CNI with sirolimus, mycophenolate with low dose prednisolone, or mycophenolate alone (in rare cases).

In general the following strategy seems sensible, but there is no current evidence base.

In patients with a tacrolimus trough of >5µg/L, in the first instance commence mycophenolate mofetil 750mg-1g bd and reduce tacrolimus dose to a trough of <5µg/L.

In patients with a tacrolimus trough consistently <5µg/L, consider stopping the CNI completely and replacing with an alternative:

- In patients **without proteinuria*** sirolimus may be the best option especially in patients with poorly controlled diabetes (sirolimus should be commenced as outlined above).
- In patients with **proteinuria*** switch to mycophenolate mofetil 750mg-1g bd plus long-term prednisolone 10mg od (potentially reducing to 5mg od in the long-term)

Adverse effects of mycophenolate – consider switching to azathioprine.

*The criteria for clinically significant proteinuria have been changed from a urinary ACR of ≥30mg/mmol (equivalent to urinary protein excretion of 0.5g/24 hours) to ≥3mg/mmol because there is evidence that the risk of adverse outcomes is a continuum and starts at an ACR well below 30mg/mmol.

Avoid sirolimus in patients with a urinary ACR ≥30mg/mmol and use with caution if ≥3mg/mmol.

13.5 Treatment of acute cellular rejection (ACR)

13.5.1 First episode

Methylprednisolone 500 mg IV daily for three days as dictated by liver biopsy (moderate or severe).

If liver biopsy is not feasible due to coagulopathy/clinical condition, treatment for acute cellular rejection may be instituted without a liver biopsy – this decision to be made by consultant hepatologist and transplant surgeon on an individual basis. Other immunosuppression should be increased in tandem (e.g. increased tacrolimus dose/addition of a second agent).

Consider switching azathioprine to mycophenolate.

13.5.2 Second episode

If no biochemical response repeat liver biopsy. If ongoing rejection, give further treatment with methyl prednisolone 500 – 1000mg IV daily × 3 doses.

13.5.3 Steroid resistant rejection and antibody-mediated rejection (AMR)

Steroid-resistant acute cellular rejection is defined as absence of response to two courses of IV methyl prednisolone. If significant vascular component request C4d stain and donor specific antibody (DSA) screen.

Antibody mediated rejection (AMR) is currently diagnosed in the presence of positive DSA and histological features compatible with antibody mediated rejection (which may include C4d staining). DSA are not 100% sensitive or specific for AMR and nor is C4d staining. It is notable that AMR remains an unclear entity and the implications and management remain unclear.

Treatment of AMR:

- Triple immunosuppression (CNI, MMF, prednisolone)
- 5 days plasma Exchange (potentially with subsequent IVIg) with serum sample to tissue typing taken pre-first and post-last exchange
- DSA assays performed at baseline and pre- and post-exchange on days 4 and 5
- If no response to plasma exchange then stop – if responding then continue consecutively until nadir is reached
- Alemtuzumab (Campath®) can be considered following plasma exchange. A suggested dose is one or two doses of 30mg **subcutaneously only**.
    - If using, there should be pre-medication with hydrocortisone and chlorphenamine with antimicrobial prophylaxis as for anti-thymocyte globulin.

13.5.4 Anti-thymocyte globulin (Thymoglobulin®)

In patients with rejection refractory to methylprednisolone many patients will respond to high dose tacrolimus and mycophenolate mofetil. Rabbit anti-human thymocyte globulin (ATG e.g. Thymoglobulin®) is an option. In patients who have previously been exposed to

rabbit ATG or who are allergic on test dose, or known to be allergic to rabbits, consider using alemtuzumab (Campath®).

Administration of ATG needs to be supervised closely. In patients with fluid overload the first dose has been known to precipitate fatal pulmonary oedema (due to cytokine release making lung capillaries leaky). Hence:
The patient must be reviewed by a senior member of staff (SpR/consultant) before ATG is given. If pulmonary oedema is present (CXR), it requires treatment, almost certainly by dialysis, before treatment with ATG commences.
The test and first dose of ATG should be administered under close observation.

Prescribe test dose
Thymoglobulin® 5 mg (1 ml) in 100 ml of 0.9% saline, IV over one hour.

Watch for signs of anaphylaxis
Signs of anaphylaxis are:
- swelling of lips, tongue, and pharynx
- bronchospasm
- hypotension.

If these occur:

- stop ATG infusion if still running
- call senior medical cover (hepatology SpR/ on-take medical SpR) immediately
- ensure airway is patent (if not, call 2222)
- lay patient flat (helps BP)
- give 100% oxygen
- give adrenaline 0.5-1 mg IM (0.5-1 ml of 1/1000), repeated every 10 minutes as necessary, and then
- give chlorpheniramine 20 mg IV and hydrocortisone 200 mg IV to prevent recurrence.

Note that minor reactions such as fever, rigors and rashes are not a contraindication to commencing the therapeutic dose.

If test dose is tolerated:

If test dose is tolerated proceed directly to prescribe:
hydrocortisone 100 mg IV and chlorpheniramine 10 mg IV 30 minutes before:
thymoglobulin 1.5 mg/kg rounded to nearest 25mg vial in 50-100 ml of 0.9% saline or 5% glucose, given IV into a central line over 6 hours (for the first dose, subsequently this may be reduced to 4 hours) as per IV monograph.

Standard course

Duration of treatment depends on patient's response. Typically a maximum of 14 days is given. Requirement for further dose is reviewed daily – if lymphocyte count < 0.05 do not give (see instructions below):

Lymphopaenia is generally observed from the second or third day of treatment onwards. Daily monitoring of the lymphocyte count is required, with the intention that this should be reduced to below 50 cells/microlitre (0.05×10^9/l).

A dose of 1.5 mg/kg of thymoglobulin rounded to nearest 25mg vial should be given on each day that the lymphocyte count is above 0.05×10^9/l, provided that:

- the total white cell count is above 2.5×10^9/l, and
- the platelet count is above 80×10^9/l.

If the white cell count is $<2.5 \times 10^9$/l or the platelet count $<80 \times 10^9$/l the dose of ATG should be reduced to half normal, and if the white cell count is $<1.5 \times 10^9$/l or the platelet count $<50 \times 10^9$/l the use of ATG should be suspended.

The dose of ATG may be increased if the lymphocyte count fails to fall.

The first dose of ATG frequently induces a reaction – fever, rigors, rash. With subsequent doses this is less common. Pre-medication with hydrocortisone and chlorpheniramine prior to each dose remain recommended.

Note:

- Azathioprine or MMF should be stopped when patients are lymphopaenic (below normal range) with ATG treatment.
- Patients at high risk of CMV infection (negative recipient of positive organ) are likely to develop severe symptomatic disease if they receive antibody treatment for rejection. If patients are given ATG they should also receive treatment dose valganciclovir.
- CMV positive recipients, or negative recipients exposed to CMV, should receive valganciclovir prophylaxis
- All patients should receive fluconazole prophylaxis during administration.
- All patients should receive PJP prophylaxis – co-trimoxazole 480mg 3 times weekly (Mon, Wed, Fri) for six months.

14 Hepatitis B prophylaxis/ treatment

Prophylaxis against Hepatitis B infection of the graft is performed through the combined use of an oral nucleoside analogue and concentrated hepatitis B immunoglobulin (HBIg).

14.1 Hepatitis B positive recipients

14.1.1 Risk assessment

Low risk = HBV DNA undetectable at the time of transplant andAND no HIV/HDV co-infection and, no history of resistance to oral HBV treatments.

High risk = HBV DNA detectable at the time of transplant, any patients with HDV co-infection, any patients with a history of resistance to oral HBV treatments

14.1.2 Intra-operative management

All patients should receive 5000 units HBIg IV (Hepatect®) day 0 during the anhepatic phase and 5000 units IV immediately post operatively on ICU.perioperatively; This should be dispatched to theatre with the patient. A supply will be kept in the fridge on F5 HDU, otherwise it can be obtained via ward pharmacists Monday- Friday 9-5pm via secure chat transplant (pharmacy) group or from pharmacy as per critical drugs contacts on Connect.

The initial rate of infusion is 0.1ml/kg/hour increased if tolerated to 1ml/kg/hour. It is recommended that the infusion should be started before or at the beginning of the anhepatic phase.

Low risk patients: Do not require any further HBIg

High risk patients: 5000 units should be given on post-op day 2.Recheck anti-HBs day 3, on day 4/5 if day 3 anti-HBs result <500 mIU/ml give 5000 units HBIg IV From day 7 give 500 units of HBIg subcutaneous (Zutectra®) weekly or two weekly as per 14.1.2. Continue to check anti-HBs at each outpatient visit in the early stages, or weekly if still an inpatient, target > 100 mIU/ml

Oral nucleos(t)ide analogue treatment:

All cases should either continue their anti-viral regimen or commence entecavir 0.5 mg daily or tenofovir 245mg (adjust for renal function) from day one post-op.

Tenofovir disoproxil
Note: Reduce dose of tenofovir in renal impairment:

Renal function	Maintenance dose	Dose interval
eGFR >50 ml/min	245 mg	Daily
eGFR 30 - 50 ml/min	245 mg	Every 2 days
eGFR 10 - 30 ml/min	245 mg	Every 3 days
eGFR < 10 ml/min	245 mg	Weekly
RRT	245 mg	Weekly

Entecavir
Note: Reduce dose of entecavir in renal impairment (on occasion, 1mg dosing may be recommended):

Renal function	Maintenance dose	Dose interval
eGFR >50 ml/min	0.5 mg	Daily
eGFR 30 - 50 ml/min	0.5 mg	Every 2 days
eGFR 10 - 30 ml/min	0.5 mg	Every 3 days
eGFR < 10 ml/min	0.5 mg	Every 7 days
RRT	0.5 mg	Every 7 days

14.1.3 Long term management

From day 7 post-op patients should be converted to subcutaneous HBIg (Zutectra® 500 units/mL) 500 units every one or two weeks to maintain anti-HBs target >100 mIU/ml, intiate at a weekly dose. Patients should be taught how to self-administer prior to discharge. Assessment of anti-HBs levels at every clinic appointment initially, to be maintained at >100Miu/ml Dosing should be adjusted according to levels with a usual maintenance dose of 500 units weekly or fortnightly, the frequency may be lower than this as levels dictate- see below for suggested adjustments. Patients should bring the dose with them to each outpatient consultation if clinic assisted administration is needed, this should be in a cool box (please arrange with liver coordinators in advance), a sharps bin will be provided from the ward at discharge. High risk patients will receive 6 months of HBIg and long term oral anti-viral therapy unless they are delta positive where at least 12 months of HBIg AND negative HBsAg and HDV RNA undetectable, is recommended in conjunction with specific input from hepatitis team when stopping. Low risk patients do not need HBIg at discharge.

14.1.4 Medication supplies

Relevant patients will be discharged with 10 syringes as standard. The transplant pharmacy team will email the liver coordinators via add-tr.livertransplant@nhs.net to advise of this.
The CNS liver coordinator or consultant needs to contact transplant pharmacy via cuh.transplant.pharmacy@nhs.net or secure group chat Pharmacy (transplant) to request re-supplies for outpatients ideally prior to patients running out.

Due to high cost and short expiry limited stocks are kept, as a result the outpatient pharmacy do not stock this- please do not route prescriptions to outpatient pharmacy as they will not be processed.

Due to need for refrigerated storage, outpatient requests for patients followed up at outreach centres will need to be couried if there is no facility for provision from the outreach centre.

Suggestion for frequency adjustment- if anti-HBs >500 units- please contact the transplant pharmacy team for advice on adjustments- extending the dosing interval by at least a week

can be considered with repeat lab tests two weeks later. HBIg has a long half-life (3-4 weeks), therefore will take time to reach steady state.

14.2 HBcAb+ HBsAg- donors

For HBV naïve recipients, oral anti-virals should be prescribed as documented above with three monthly monitoring of HBsAg and HBV DNA. For those with an anti-HBsAg titre >100 mIU/ml at one year, oral anti-virals may be stopped, but monitoring for *de novo* HBV 3 monthly continued for at least one year and then at every clinic visit thereafter.

14.3 HBcAb+ HBsAg- recipients

Anti-HB core positive/ HBsAg negative recipients receiving non-HBV donors do not require prophylaxis, but should be monitored with 3 monthly HBsAg and HBV DNA levels for at least one year and at every clinic visit thereafter.

15 Management of long-term graft related complications

15.1 Screening

15.1.1 Ischaemic cholangiopathy

Patients (DBD or DCD graft recipients) will not undergo routine surveillance MRCPs for ischaemic cholangiopathy.

15.1.2 Hepatocellular carcinoma

Recurrent HCC
All patients found to have hepatocellular carcinoma on the explant with any of the following adverse features will have 6 monthly CT chest/abdo/pelvis and AFP (if pre-transplant tumour was AFP positive) until 4 years post-transplant to screen for recurrent disease:

- Moderately differentiated tumours (by explant histology)
- Poorly differentiated tumours (by explant histology)
- Lymphovascular invasion present (by explant histology)
- Three of more tumours identified pre-transplant
- AFP-positive tumours

Patients with none of the above (primarily those with low-risk, well-differentiated tumours) not undergo screening.

De novo HCC
Patients who develop graft cirrhosis will have standard HCC surveillance with 6 monthly ultrasound and AFP.

15.2 Investigation of graft dysfunction

Abnormal liver blood tests are frequently encountered after liver transplantation. Interpretation should take into account the clinical context, in particular, timing in relation to transplantation and chronicity. Aetiology may be transplant specific, but non transplant related causes should also be considered.

See appendix 4.

15.3 Management of biliary drainage

Biliary reconstruction will generally be either a duct-to-duct anastomosis or a Roux limb hepaticojejunostomy.

Prophylactic antibiotics for cholangiogram/ERCP or biliary surgery:
co-amoxiclav 1.2g IV pre procedure; if penicillin resistant ciprofloxacin 750 mg PO plus metronidazole 400mg PO. If ESBL colonised, use meropenem 1g IV instead; or if known MRSA positive, add vancomycin 1g IV.
If resistant Gram negative organisms are present contact microbiology for advice.

Penicillin allergic patients: ciprofloxacin 400 mg IV plus vancomycin 1000 mg IV plus metronidazole 500 mg IV.

For management of possible biliary stricture see appendices for management algorithm.

15.4 Treatment and prevention of disease recurrence

15.4.1 Hepatitis B

See the hepatitis B prophylaxis/ treatment section above.

15.4.2 Hepatitis C

Most patients will be HCV RNA negative by the time of transplantation. For those who are not, a plan should have been made for timing of treatment at the time of liver transplant listing.

For HCV RNA +ve recipients: Patients will no longer require protocol liver biopsies. Graft fibrosis may be monitored with Fibroscan® from 1 year post transplant. Patients will be eligible for treatment based on national guidelines, which are available at http://www.easternliver.net.

For patients with hepatitis C coming to transplant on antiviral drugs, interactions may be significant. Interactions can be checked by contacting the pharmacy team or by accessing the Liverpool University Hep C drug interaction reference site at: http://www.hep-druginteractions.org/.

15.4.3 Autoimmune chronic active hepatitis (alloimmune hepatitis)

Patients transplanted with this primary liver disease require long-term dual immunosuppression. If persistently deranged liver blood tests, check serum immunoglobulins and consider biopsy to exclude alloimmune graft injury.

15.4.4 Primary biliary cholangitis

Usually require long-term dual immunosuppression.

Once stabilised post-transplant, commence UDCA 13–15 mg/kg/day long-term as prophylaxis to reduce risk of recurrent disease.

Consider second-line therapies such as obeticholic acid for those with ongoing elevated alkaline phosphatase despite UDCA.

15.4.5 Primary sclerosing cholangitis

Usually require long-term dual immunosuppression. If persistently deranged liver blood tests, consider biopsy/MRCP. If evidence of recurrent PSC consider UDCA 13–15 mg/kg.

For PSC alone and normal histology throughout colon: one-off surveillance colonoscopy with biopsies at five years. In patients with co-existent colitis ensure annual surveillance colonoscopy or pouchoscopy.

15.4.6 Hepatocellular carcinoma

There is currently no convincing evidence to support the use of sirolimus to prevent or delay recurrence of hepatocellular carcinoma post-transplant.

15.4.7 Alcohol-related liver disease

Ideally all patients transplanted for alcohol-related liver disease should have long term follow up with an addiction specialist.

Random ethanol levels should be sent at every opportunity (consent for this will be provided when signing the alcohol agreement at time of listing).

Patients transplanted for alcohol-related liver disease are at higher risk of upper aero-digestive cancers. Symptoms reported at clinic appointments should be noted with this in mind.

15.4.8 Metabolic dysfunction-associated steatohepatitis (MASH) cirrhosis

Optimal control of the metabolic syndrome and lifestyle measures (see “Management of long-term metabolic and cardiovascular risk factors”).

Weight gain is common after liver transplantation. One of the major risk factors for weight gain post-transplantation is obesity pre-transplantation.

A key aspect of management of patients transplanted for MASH cirrhosis (+/- HCC) is to educate about the risk of weight gain and worsening metabolic problems with a high risk of dying from cardiovascular disease and obesity-related cancers.

16 Management of long-term infection complications

16.1 Bacterial

Sepsis should be considered in cases with pyrexia, rising WCC or CRP, unexplained cholestasis or other deterioration in LFTs.

The differential diagnosis for pyrexia in a post-transplant recipient includes rejection, hepatic artery thrombosis, CMV, pulmonary emboli, and at a later stage, post-transplant lymphoproliferative disease (PTLD).

Patients should have:
- Peripheral/central cultures
- Sputum/fresh drain fluid/urine +/- stool cultures
- IV line site/inflamed wound site swab
- Blood for CMV PCR (if donor or recipient is positive)
- CXR; if chest X-ray is abnormal or respiratory symptoms present request nose, throat swabs for respiratory viruses and urine legionella antigen
- Repeat ultrasound/doppler.

Further abdominal/chest imaging may be required depending on clinical picture and will be guided by the hepatology consultant/transplant surgeon.

Empirical treatment of sepsis post-liver transplant:

Piperacillin-tazobactam 4.5g IV tds

If hypotensive or critically ill consider a single dose of amikacin IV 15mg/kg (reduce for renal impairment as per http://merlin/Lists/DMSRecords/DispRecordTabsDoc.aspx?ID=21035&IsDlg=1&Source=/&IsDlg=1#) depending on culture result. Discuss with Microbiology if concerns with renal function.

Further management:

- **Review antibiotics at 48h**
- If positive cultures – rationalise with susceptibilities
- If negative cultures but clinically improving - continue antibiotics with daily review, with a view to rationalising to PO antibiotics by day 5 or earlier
- If negative cultures but clinically deteriorating / not improving - Senior review
    - Consider viral infections e.g. CMV, adenovirus, herpesviruses, other respiratory viruses and non-infective causes of fever
    - Send repeat septic screen
    - Escalate therapy to Meropenem 1g TDS and if improving clinically, complete a further 5 days' treatment
    - For patients with pneumonia consider BAL (and add atypical cover if admitted from the community – care with clarithromycin – see interactions section)
    - If line infection suspected, consider removal
- It is important to achieve source control early – if abscess /collection present, request for prompt drainage
- Consider the donor as a potential source.

Infection / colonisation with multi-resistant organisms (e.g. CPE / ESBL / VRE / MRSA)

Infection or colonisation with any of these organisms (either in Addenbrooke's or their host trust) should lead to discussion with infection control and microbiology, ideally before transplant so appropriate prophylaxis can be commenced (see below)

16.2 Clostridium difficile

(see separate Trust Guidelines for more details)
C difficile should be excluded in patients with new diarrhoea post-transplant.

In the case of *C. difficile* infection, standard infection control measures should be implemented as per Trust policy.

Treatment should be as per the trust guidelines.

Consider whether the case meets criteria for either severe disease* or recurrent disease**

*Severe disease defined as any of: temp >38.3 °C; albumin <25 g/L, WCC >15 $\times 10^9$/L, CRP >200 mg/L, lactate >2.4 mmol/L, bowels open >6/24 hours, acute kidney injury, colitis, haemodynamic instability
** recurrent episode = 3rd or more

All patients require a baseline AXR.

If no improvement after 48 hours, involve the MDT (ID SpR)

Some patients may require a flexible sigmoidoscopy to clarify the diagnosis.

Consider the possibility of co-existing CMV colitis.

16.3 Cytomegalovirus

(see separate trust guidelines for more details)
Valganciclovir prophylaxis is given to liver transplant recipients with 'CMV mismatch': donor CMV+ / recipient CMV– (D+R-, see under "Post liver transplant prophylaxis" section).

Patients with D+/R+ and D-/R+ should have weekly CMV PCR during hospitalisation and then at every attendance at clinic. D-/R- do not require screening and should only have a CMV PCR sent if clinical suspicion of CMV disease (e.g. unexplained pyrexia, transaminitis, leucopenia, diarrhoea).

CMV infection = CMV replication in any body fluid or tissue specimen whether or not symptoms present.

CMV disease = as above but with clinical manifestations associated with CMV i.e. CMV syndrome and end-organ disease.

CMV syndrome = a combination of fever and bone marrow suppression. May present as one or more of: temp >38°C, malaise, leucopaenia, thrombocytopenia, elevated liver enzymes.

End-organ disease = include pneumonitis, gastrointestinal disease (including pancreatitis and colitis), hepatitis, CNS disease and chorioretinitis.

Patients with primary infection are at greatest risk of developing CMV disease. Viral load in plasma also correlates.

Diagnosis:

CMV PCR of blood +/- BAL fluid and biopsy; CSF; histology (CMV inclusions) (also send biopsy for CMV PCR)

Management:

Management is decided on a case-by-case basis – **if viraemic inform the hepatology consultant.**

CMV viraemia will in most cases respond to a reduction in immunosuppression (Aza/MMF may need to be stopped). The viral load should be monitored weekly if an inpatient, or every time they are seen in clinic. If persistent significant viraemia (>5000 iu/ml) despite this, or when the immunosuppression cannot be reduced, oral treatment dose valganciclovir may be considered. Anti-CMV therapy should also be given if the viral load increases by >0.5 log10 between samples.

All patients with symptomatic disease should be commenced on treatment promptly.

If the patient is well enough to be treated as an outpatient then oral valganciclovir (900mg bd, adjusted for renal function) can be considered.

All patients with significant symptoms/end-organ effects require hospital admission.
IV ganciclovir is preferred in patients with severe or life-threatening disease or in patients with poor gastrointestinal absorption. Give IV ganciclovir (doses below) for a minimum of 2 weeks, followed by valganciclovir 900mg bd.

CMV disease is treated (with ganciclovir or treatment dose valganciclovir) until:

- Clinical resolution of symptoms, and
- 2 consecutive negative CMV PCRs, and
- Minimum of 2 weeks treatment

Secondary prophylaxis with valganciclovir 900mg od (adjusted for renal function) may then be initiated for a total duration of 3 months.

Foscarnet is an option in patients who do not respond, but has the potential for ophthalmic toxicitynephrotoxicity and electrolyte derangement, and should be avoided in significant renal impairment. Discuss with the virologists prior to use.

Maribavir is a 2nd line PO therapy in resistant or refractory disease as per separate trust protocol for CMV in solid organ transplant and NICE TA. Note potential interacions with calcineurin inhibitors- see interaction section for detail.

Valganciclovir and ganciclovir dose varies according to renal function.

For valganciclovir (according to manufacturer's data sheet):

Creat clearance (ml/min)	**Treatment dose**	**Prevention dose**
≥ 60	900 mg twice daily	900 mg once daily
40 – 59	450 mg twice daily	450 mg once daily
25 – 39	450 mg once daily	450 mg every 2 days
10 – 24	450 mg every 2 days	450 mg twice weekly
< 10	Discuss with pharmacy	Discuss with pharmacy

For Ganciclovir (according to manufacturer's data sheet):

Creat clearance (ml/min)	**Ganciclovir treatment dose (intravenous)**
>70	5 mg/kg BD
50-69	2.5 mg/kg BD
25-49	2.5 mg/kg OD
10-24	1.25 mg/kg OD
<10	1.25 mg/kg three times a week, after haemodialysis

Dilute in 100 ml of 0.9% saline or 5% glucose and give over one hour.

Note adjusted dosing regimens may be used according to renal drug handbook, see trust guideline. Discuss with a transplant or critical care pharmacist dosing in continuous renal replacement therapy.

If switching from IV ganciclovir to PO valganciclovir, 5mg/kg ganciclovir is equivalent to 900mg of valganciclovir.

17 Management of long term metabolic and cardiovascular risk factors after liver transplantation

Patients should be encouraged to develop a good relationship with their GP from early post-transplant. **Primary care play an invaluable role** in the management of the metabolic syndrome and can provide additional psychological support.

Shared care is also encouraged with their local Gastroenterologist/Hepatologist. Referral to other specialities should be requested via the GP and within their local NHS Trust in most cases.

17.1 Hypertension

See NICE guidance CG87 2009, CG 127 2011, CG 182 2014, NG136 2019.

Target systolic blood pressure is <140/90 mmHg (<150/90 mmHg if >80 years old); in patients with “white coat effect” <135/85 mmHg on ABPM or HBPM; in uncomplicated diabetes <140/80 mmHg, but in diabetes + renal/ eye/ cerebrovascular disease 130/80 mmHg; in chronic kidney disease 140/90 mmHg, but in the presence of diabetes or a urinary ACR >70 mg/mmol 130/80 mmHg.

Systolic blood pressure is a stronger risk factor for cardiovascular disease than diastolic pressure.

Amlodipine is preferred initial treatment: start at 5 mg daily. Expect 25% to get ankle oedema – more likely at a higher dose.

Second-line treatment is an ACE inhibitor. If ACE inhibitor not tolerated, try angiotensin receptor blocker (ARB).

17.2 Hyperlipidaemia

See NICE CG181 (2014) for Lipid Modification and Cardiovascular Risk assessment

Full lipid profile to be checked at:
- one month
- three months
- six months
- six-monthly thereafter.

Bearing in mind the increased cardiovascular risk of liver transplant recipients and the almost universal occurrence of chronic kidney disease (see below), a Statin will be offered to all patients aged ≥50 years. In patients <50 years, adhere to the NICE guidelines.

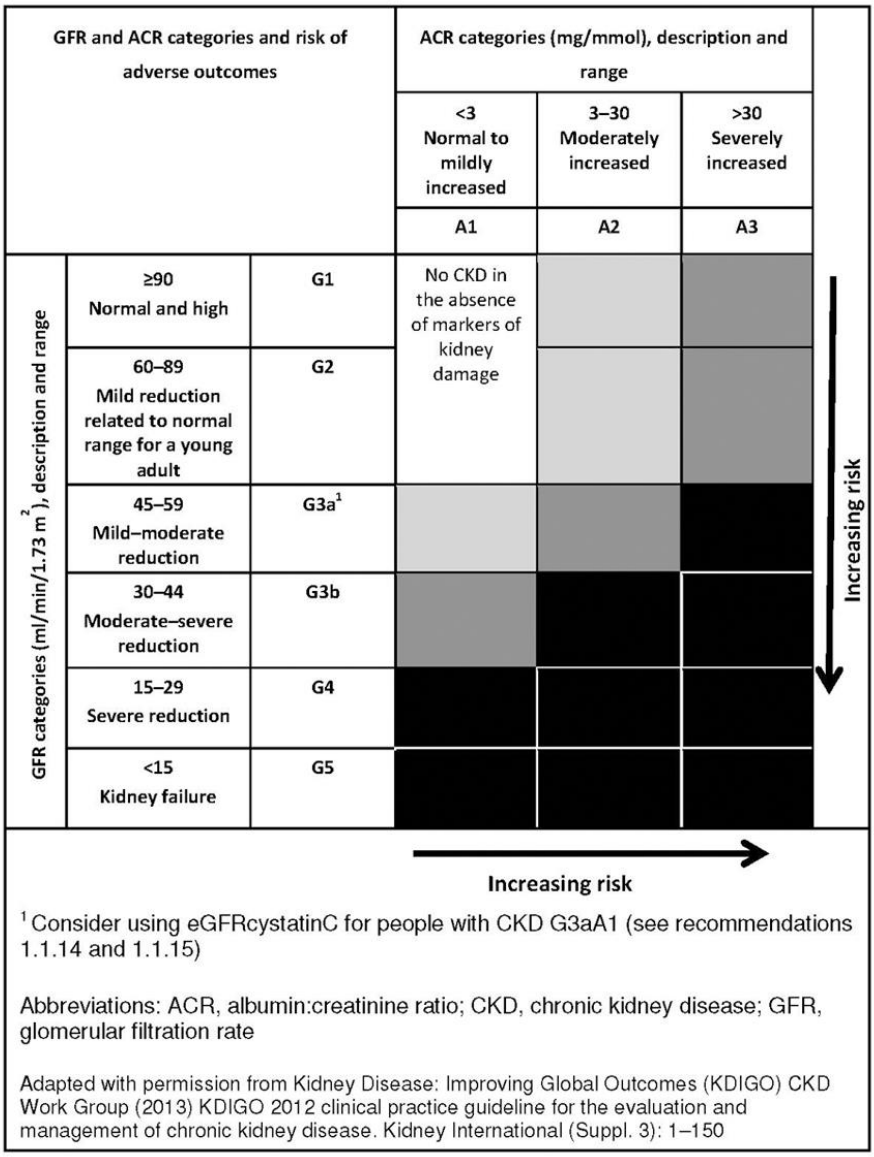
Pravastatin is statin of choice in the context of ciclosporin use as not liver-metabolised. In tacrolimus, standard statin choice applies.

If hypertriglyceridaemia – fibrates and/or ezetemibe can be used.

17.3 Renal dysfunction

See NICE guidance CG 182 2014.

Chronic kidney disease (CKD) is characterised by the presence of markers of kidney damage regardless of the GFR; and in patients with a GFR<60 on at least 2 occasions separated by a period of 90 days (with or without markers of kidney damage e.g. urinary ACR >3 mg/mmol; abnormalities on histology or imaging).



[1] Consider using eGFRcystatinC for people with CKD G3aA1 (see recommendations 1.1.14 and 1.1.15)

Abbreviations: ACR, albumin:creatinine ratio; CKD, chronic kidney disease; GFR, glomerular filtration rate

Adapted with permission from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group (2013) KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney International (Suppl. 3): 1–150

All patients should have U&Es, a urinalysis, and a urinary ACR checked (regardless of eGFR) on at least an annual basis (urine dipstick has a low sensitivity for microalbuminuria).

A urinary ACR of 3 mg/mmol or more is clinically significant.

Persistent invisible haematuria (at least 2++ on urinalysis) with/without proteinuria should precipitate referral to urology.

A renal ultrasound scan is indicated when:

- There is an accelerated rate of progression of CKD (a sustained reduction in GFR of >25% and a change in GFR category within 12 months or a sustained reduction in GFR of 15 per year).
- Visible or persistent invisible haematuria
- Symptoms of UTI
- eGFR <30 mL/min/1.73m^2

Management:
- Excellent blood pressure control (if any CKD aim for <140/90; if CKD with diabetes or urinary ACR >70mg/mmol aim for <130/80).
- An ACE is preferred if diabetic and urinary ACR >3; hypertensive and ACR >30; ACR>70
- All patients with any CKD should be offered a statin

Patients should be referred to a nephrologist if:
- eGFR <30
- eGFR <60 and urinary ACR >30 and/or uncontrolled hypertension
- Nephrotic (urinary ACR >220)

17.4 Anti-thrombotic treatment

All patients are discharged on aspirin 75mg od long-term given the increased cardiovascular risk of liver transplant recipients and to reduce the risk of hepatic artery thrombosis.

Some patients will be considered at higher risk of graft vessel thrombosis and will receive long-term formal anti-coagulation: treatment dose dalteparin initially converted to oral anti-coagulation after 3 months (see below). Risk status will be determined by the transplant surgeon and hepatologist and will take into account pre/peri-transplant vessel thrombosis, anatomy, recipient procoagulant state.

Warfarin is safe and remains the first line oral anti-coagulant post-transplant.

Novel anticoagulant (DOAC) drugs (see appendix 6):

- The safety of the DOACs remains unclear in liver transplant recipients.
- Dabigatran is contraindicated in patients on ciclosporin and not recommended with tacrolimus because of interactions.
- Ciclosporin is likely to interact resulting in increased blood levels of apixaban and rivaroxaban. Tacrolimus and sirolimus are unlikely to result in a clinically significant interaction. However, there is one recent case report of GI haemorrhage in a patient treated concurrently with rivaroxaban and Tacrolimus.
- In patients with creatinine clearance <30ml/min rivaroxaban plasma levels may be significantly increased (1.6 fold). Use is not recommended when <15ml/min.

17.5 Diabetes mellitus

See NICE CG87 (2014) for Diabetes Management

Random glucose and HbA1c is monitored at each attendance at the transplant clinic (**remember HbA1c may be falsely low in patients with anaemia**).

If evidence of a new diagnosis of Diabetes Mellitus, inform GP as a matter of urgency.

Manage as per the NICE guidelines.

Standard oral hypoglycaemic agents (OHAs), as well as newer agents such as pioglitazone, GLP-1 analogues (e.g. liraglutide), DPP-4 inhibitors (e.g. sitagliptin) and SGLT2-inhibitors (e.g. dapagliflozin) can be used in transplant patients.

Targets of glycaemic control, BP and lipid control should be as for the non-transplant population.

Encourage GPs and patients to use Statins if indicated by QRISK3 score.

17.6 Hyperuricaemia

If uric acid greater than 0.45 mmol/L consider allopurinol 100 mg/day.

Allopurinol significantly increases the effect of azathioprine. Attempt to avoid this combination if at all possible through the use of mycophenolate instead of azathioprine. azathioprine should be stopped 2 weeks before starting the allopurinol. If azathioprine cannot be stopped, the dose of azathioprine should be **reduced by 75%** whilst co-prescribed, and the full blood count should be monitored weekly for the first 8 weeks, every 2 weeks for the next month then monthly thereafter frequency reduced if blood counts stable (myelosuppression has been observed up to 3 months after starting concurrent therapy).

Colchicine 0.5 mg bd alternative for gout if allopurinol intolerant. Febuxostat via GP can be provided for patients with hyperuricaemia, who are refractory to, or intolerant of, allopurinol. Concurrent azathioprine should be avoided with febuxostat wherever possible. If not possible dose reduction of azathioprine is necessary with close haematological monitoring to avoid toxicity.

17.7 Bone disease

If pre-transplant DEXA osteopaenia/osteoporosis start alendronate 70mg/ week, according to instructions, or 5 mg zoledronate IV annually (if varices) as 15 min infusion. Give calcium/colecalciferol combined tablet 2 tabs daily (except day of taking bisphosphonate) alongside.

Repeat bone scan at one year and review need for bisphosphonates but continue if long term steroids.

Check testosterone level in males with osteopaenia and replace if hypogonadal.

If total 25-OH Vitamin D level is low, suggested replacement is 100 000 units of colecalciferol stat.

Treatment of vitamin D deficiency loading dose (BNF)

50 000 units once weekly for 6 weeks, alternatively 40 000 once weekly for 7 weeks, alternatively 4000 units daily for 10 weeks, different loading regimens can be used to achieve a cumulative total of approximately 300 000 units divided into daily or weekly doses over 6–10 weeks.

Treatment of vitamin D deficiency maintenance dose (BNF)

800–2000 units daily, maintenance dosing may be given daily or the equivalent dose given intermittently. Maintenance to be started one month after loading dose completed, or if correction of vitamin D deficiency is less urgent, maintenance may be started without the use of loading doses. Higher maintenance doses may be necessary in those at high risk of vitamin D deficiency; maximum 4000 units per day.

18 De novo cancer post-transplant

All patients undergoing liver transplantation should be advised about the increased risks of cancer after transplantation.

Expect total abstinence from alcohol in patients transplanted for alcohol-related liver disease, and minimal alcohol consumption in other patients. Abstinence from tobacco smoking is strongly recommended.

Patients should partake in the national bowel cancer and breast cancer screening programs as per the general population.

In patients with primary sclerosing cholangitis and co-existent colitis ensure annual surveillance colonoscopy or pouchoscopy.

Women should have cervical screening in accordance with national guidelines for the non-immunosuppressed. Similarly, any patient with a previous history of CIN should have routine follow-up in accordance with the guidelines for the immunocompetent (NHSCSP guidelines: https://www.gov.uk/government/publications/cervical-screening-programme-and-colposcopy-management)

Patients should be given appropriate advice and encouraged to look for new skin lesions. Medical advice should be sought promptly for new lesions.

Sirolimus may reduce the risk of non-melanoma skin cancers, but its role in other malignancy is yet to be established (https://www.ncbi.nlm.nih.gov/pubmed/25422259).

19 Relevant common transplant drug interactions

This list covers the **common interactions** involving immunosuppressant drugs seen routinely for newly transplanted liver transplant recipients and existing liver transplant recipients while they are **inpatients.**
The ability to appropriately monitor and manage interactions must be further considered for outpatients due to the relative difficulty in measurement and interpretation of blood levels. Please contact the transplant pharmacy team via secure chat (Pharmacy (transplant) group) for inpatients and urgent outpatient queries or cuh.transplant.pharmacy@nhs.net for outpatients if non-urgent specialist advice is required for specific patients.

Caution: this list is not exhaustive. The absence of a drug in this list does not indicate that there is no interaction.

Key

+	interaction of low clinical importance
++	interaction of medium clinical importance
+++	interaction of high clinical importance
AED	Anti-epileptic drug
AKI	Acute kidney injury
CNI	Calcineurin inhibitor
DAA	Direct-acting antiviral
DOAC	Direct-acting oral anticoagulant drug
ESRF	End-stage renal failure
FBC	Full blood count
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IV	Intravenously
PO	Orally
QDS	Four times daily
SmPC	Summary of product characteristics
SS	Steady state. This is the time taken to reach a steady state level in the blood after initiation, dose change, or stopping of a drug. It is the product of 4.5 x half-life.
T ½	Half-life. This is the time taken for the blood concentration of a drug to fall by 50%
TDS	Three times daily

Half-lives and estimated time to steady state of common immunosuppressant drugs

Drug	Estimated half-life (T½)	Estimated time to steady state (SS)
Ciclosporin (Neoral)	**5 – 20 hours**	**22.5 – 90 hours**
Sirolimus	**48 – 78 hours**	**216 – 351 hours (Effective half-life reached after 5 – 7 days according to the SmPC)**
Tacrolimus	**12 – 16 hours**	**54 – 72 hours**

19.1 Azathioprine with allopurinol or febuxostat

Significant interaction - A 75% reduction of the azathioprine dose is needed and close monitoring of full blood count (FBC) is required. Dose reduction does not always prevent the development of haematological toxicity. A switch of azathioprine to mycophenolate mofetil should be considered.

Due to the long T ½ of allopurinol and its active metabolite, a 2 week wash-out period from stopping allopurinol to starting azathioprine should be used. If a switch to mycophenolate mofetil is not possible and allopurinol must be continued, azathioprine dose reduction as above and very close FBC monitoring will be needed.
Febuxostat interacts in a similar way, but the size of the azathioprine dose reduction with concurrent use is less predictable. The combination should be avoided whenever possible due to the risk of neutropenia.

19.2 Calcineurin inhibitors

Interactions resulting in increased levels of calcineurin inhibitors (CNIs) (ciclopsorin, sirolimus and tacrolimus)

Drug	**Onset**	**Clinical importance**	**Suggested Management**	**Comments**
Apixaban	See under DOACs			
Clarithromycin	See under macrolides			
Direct-acting activated factor X inhibitors (DOACs) Including apixaban edoxaban rivaroxaban		+ Case reports for tacrolimus only	Monitor tacrolimus levels daily on initiation and following discontinuation as a precaution.	Possible increased risk of bleeding (tacrolimus and ciclosporin only) as DOAC levels may be increased.
Edoxaban	See under DOACs			
Erythromycin	See under macrolides			
Fluconazole	T½ 30 hours (98 hours in ESRF). Onset may occur within 3 days. 6 days to reach SS after starting,	+ to ++ Considerable interpatient variability	Monitor **tacrolimus and ciclosporin** levels closely and adjust dose as needed. If blood levels are significantly elevated consider alternative antifungal e.g. anidulafungin (not caspofungin).	Extent of interaction is fluconazole dose dependent. A 400mg dose has a much bigger inhibitory effect than a 100mg dose. Prospective tacrolimus or ciclosporin dose adjustment is not usually recommended with standard fluconazole prophylaxis due to the potential for sub-therapeutic

	stopping or dose change.		**Sirolimus** - avoid combination if possible; otherwise consider a 50% prospective dose reduction of sirolimus. Consider risk of QT-interval prolongation.	levels. Consider the clinical scenario. Plan for standard fluconazole prophylaxis to stop (if appropriate) several days in advance of discharge to avoid unstable levels following discharge
Macrolides Including clarithromycin and erythromycin	T½ erythromycin 1.5 to 2 hours. T½ clarithromycin 3 -7 hours.	++ to +++	**Erythromycin:** monitor CNI levels daily on initiation and following discontinuation of erythromycin until the interaction is stable. Difficult to manage this interaction with an outpatient **Avoid clarithromycin if possible** and explore if an alternative antibacterial is suitable. Swift rises in blood levels may be seen which could result in acute kidney injury (AKI). Difficult to manage even with dose reduction.	Erythromycin dosed as a pro-kinetic (e.g. for large gastric aspirates or in diabetic gastroparesis) is generally considered appropriate but close monitoring of levels is still required. For erythromycin treatment courses, sirolimus blood levels may be less impacted (than tacrolimus and ciclosporin) but the dose of all 3 CNIs must be carefully adjusted.
Maribavir	T½ 4.3 hours. SmPC states SS is reached after 2 days	+ to ++	Monitor CNI levels daily as inpatient on initiation until interaction stable For outpatient initiation consider twice weekly CNI level monitoring and review until steady state reached. First CNI	New drug - lack of clinical experience of interaction effect. No prospective dose reduction of CNI recommended. Should expect steady state from the interaction 2 days after initiation, dose change or discontinuation. CNI levels will reach steady state after this (or 72 hours

			level needed within 3-5 days of maribavir initiation.	after last dose change if this is later).as follows: Tacrolimus: 3 days Ciclosporin: 4 days Sirolimus: 5-7 days
Metoclopr-amide	T½ 4 – 6 hours (15 hours in ESRF)	+ to ++	Monitor tacrolimus levels on initiation until interaction stable	Due to pro-kinetic action metoclopramide may increase tacrolimus absorption by bypassing considerable intestinal wall CYP metabolism of tacrolimus.
Rivaroxaban	See under DOACs			
Voriconazole	T½ 6 hours Loading dose given; non-linear pharmaco-kinetics. SS is reached quickly.	+++ Clinically important Interpatient variability	Monitor CNI levels daily on initiation until interaction stable. **A large prospective dose reduction may be needed** as follows: • tacrolimus by 66% • ciclosporin by 50% • sirolimus by 90%. **Avoid combination with sirolimus if possible** It is very difficult to manage the interaction as an outpatient	Professional reference source (Stockley's drug interactions online) suggests a prospective reduction in CNI and sirolimus doses on initiation. However there is variability in the extent of the interaction. A large prospective dose reduction may give the risk of sub-therapeutic levels initially. **Consider the risk of under immunosuppression versus supra-therapeutic levels.** A prospective dose reduction on initiation is usually needed. **Must plan to re-optimise tacrolimus and ciclosporin dosing according to levels once voriconazole is stopped. Great care is needed with outpatients.** Consider effect of voriconazole on other concurrent drugs e.g. oxycodone.

Interactions resulting in reduced levels of calcineurin inhibitors (CNIs) (ciclosporin, sirolimus and tacrolimus)

Drug	Onset	Clinical importance	Management	Comments
Carbamazepine	Delayed enzyme induction (CYP3A4 and P-glycoprotein) when carbamazepine is newly initiated. May take from a few days to 2-3 weeks to reach maximum effect. Same delay occurs on stopping carbamazepine.	+ to +++	Importance and management depends on indication & dosing. If lower doses being used for diabetic neuropathic pain, trigeminal neuralgia or bipolar disorder compared to full dosing as an anti-epileptic drug (AED), expect a reduced interaction **Must plan to re-optimise CNI dosing according to levels if carbamazepine is stopped. Great care is needed if this is managed as an outpatient (minimum twice weekly levels).**	If carbamazepine is newly started post-transplant for seizures, consult neurology. An alternative AED should be considered wherever possible (e.g lamotrigine, levetiracetam). If taking carbamazepine pre-transplant for seizures, consult neurology to discuss potential AED alternatives. Changes in AED therapy can take time with weaning and titration of some drugs needed. This needs to be considered when patient is listed for transplant. Consider effect of carbamazepine on other concurrent drugs e.g. fluconazole, maribavir.
Phenytoin	Delayed enzyme induction (CYP3A4 and P-glycoprotein) when phenytoin is newly initiated.	+++ Clinically important	Difficult to manage when phenytoin is newly started post-transplant. A large increase in CNI dose may be needed to overcome	If phenytoin is newly started post-transplant, consult neurology. An alternative AED should be considered wherever possible (e.g lamotrigine, levetiracetam)

	May take from a few days to 2-3 weeks to reach maximum effect. Same delay occurs on stopping phenytoin.		enzyme induction. Daily CNI levels needed, then increase CNI dose to maintain level. **Must plan to re-optimise CNI dosing according to levels if phenytoin is stopped. Great care is needed if this is managed as an outpatient (minimum twice weekly levels).**	If taking phenytoin pre-transplant, consult neurology to discuss potential AED alternatives. Changes in AED therapy can take time with weaning and titration of some drugs needed This needs to be considered when patient is listed for transplant. Consider effect of phenytoin on other concurrent drugs e.g. prednisolone, fluconazole, maribavir.
Rifampicin	Delayed enzyme induction (CYP3A4 and P-glycoprotein) when rifampicin is newly initiated. May take from a few days to 2-3 weeks to reach maximum effect. Same delay occurs on stopping rifampicin.	+++ Clinically important. Applies to ciclosporin, tacrolimus and sirolimus. **The concurrent use of sirolimus is not recommended.**	Interaction is difficult to manage. May need large CNI dose increase to overcome the effects of enzyme induction. Daily CNI levels needed, then increase CNI dose to maintain level. Four-fold increase in tacrolimus dose or a three to five-fold increase in ciclosporin dose have been needed in some	Rifampicin also induces intestinal wall CYP enzymes which metabolise CNIs to a considerable extent. If rifampicin is taken immediately prior to liver transplant, it will take time for the intestinal wall enzymes to return to normal functioning. Higher initial CNI doses than usual may be needed for 2-3 weeks or longer until the intestinal wall enzymes recover to pre-rifampicin levels (assuming rifampicin is stopped)

			patients when the interaction reaches maximal effect. NB Magnitude of interaction will be smaller if being used for pruritus rather than TB treatment doses. Very difficult to manage interaction as an outpatient- not recommended to initiate in an outpatient setting if using for TB treatment	Consider effect of rifampicin on other concurrent drugs e.g. prednisolone, fluconazole, maribavir. **Must plan to re-optimise CNI dosing according to levels once rifampicin is stopped. Great care is needed if this is managed as an outpatient (minimum twice weekly levels).**

19.3 Prednisolone

Interactions resulting in reduced levels of corticosteroids (prednisolone and methylprednisolone)

Drug	Onset	Clinical importance	Management	Comments
Carbamazepine	Delayed enzyme induction when carbamazepine is newly initiated.	++	Established interaction. Patients taking carbamazepine are likely to need increased doses of methylprednisolone or prednisolone. Prednisolone is less affected than methylprednisolone.	If carbamazepine is newly started post-transplant for seizures, consult neurology. An alternative AED should be considered wherever possible (e.g lamotrigine, levetiracetam) If taking carbamazepine pre-transplant for seizures, consult neurology to discuss potential AED alternatives.
Caspofungin				
Phenytoin	Delayed enzyme induction (CYP3A4) when phenytoin is newly initiated. Same delay occurs on stopping phenytoin.	++	Difficult to manage when phenytoin is newly started post-transplant. A two-fold increase in prednisolone dose may be required. Prednisolone is less affected than methylprednisolone.	If phenytoin is newly started post-transplant, consult neurology. An alternative AED should be considered wherever possible (e.g lamotrigine, levetiracetam) If taking phenytoin pre-transplant, consult neurology to discuss potential AED alternatives.
Rifampicin	Delayed enzyme induction (approximately 14 days) if rifampicin is started. Same delay occurs	++	Difficult to manage when rifampicin is newly started post-transplant. A pre-emptive two to three-fold increase in prednisolone dose may be	

	on stopping rifampicin.		required. Dose reduction is required if rifampicin is stopped.	

19.4 Statins

Statins are usually held in patients taking them pre-admission during the immediate post transplant period. The pre-admission statin should be restarted at discharge (or earlier in patients considered at increased cardiac risk; for example following an acute myocardial infarction), unless an interaction precludes this. The risk to the patient is of muscle adverse effects, potentially severe including rhabdomyolysis.

Statin choice and dose	Tacrolimus	Ciclosporin	Sirolimus
Atorvastatin	Low risk	Maximum atorvastatin 10mg daily with close monitoring	Low risk; consider checking sirolimus level 2 weeks post-statin initiation and subsequent titration
Simvastatin	Low risk	Avoid	Initiate at low dose (10 mg daily) with monitoring for muscle side effects.
Pravastatin	Low risk	Start at pravastatin 20mg nightly with cautious titration to 40mg nightly.	Initiate at low dose (20 mg daily) with monitoring for muscle side effects.

19.5 Direct-acting antivirals (DAA); antivirals for Hepatitis C (HCV), human immunodeficiency virus (HIV) and Covid-19

Refer to the specialist online Liverpool drug interaction checkers and seek advice from the relevant specialist pharmacist (transplant/HIV/HCV) as required if antivirals are prescribed for hepatitis C, HIV or Covid-19.

https://www.hiv-druginteractions.org/checker
https://www.hep-druginteractions.org/checker
Liverpool COVID-19 Interactions (covid19-druginteractions.org)

19.6 Food interactions

Grapefruit, Seville orange and pomelo must be avoided due to potential for cytochrome P450 interactions.

19.7 Herbal remedies/supplements

Herbal remedies and supplements are sold as food items. They are not subject to interaction studies, quality testing or batch control as for licensed medicines. In general herbal remedies and supplements should be avoided in transplant recipients. **In particular, patients should be warned to avoid St John's Wort.** Known interactions with herbal remedies can be checked by Medicines Information for specific patients if required. Any potential risks to transplanted grafts or other organs from herbal remedies or supplements are outside of the scope of this document.
Queries about interactions with recreational drugs should also be referred to Medicines Information.
Queries about bodybuilding nutritional supplements or supplements for nutritional deficiencies should be directed to the dieticians.

19.8 Interactions involving prolonged QT-interval

There may be an additive effect of drugs known to prolong the QT-interval.
Note: this list is not exhaustive

- Ciprofloxacin
- Citalopram
- Clarithromycin*
- Domperidone
- Erythromycin*
- Fluconazole*
- Metoclopramide
- Ondansetron
- Tacrolimus

* May also inhibit the metabolism and increase the blood level of other drugs that prolong the QT interval

Important Drug Handling Issues
Low Albumin
Tacrolimus is >98% plasma protein bound and only the unbound (free fraction) is active. Reduced levels of major proteins for drug binding potentially mean there is a greater free (active) fraction). This is not accounted for by the reported tacrolimus level, as only the total tacrolimus level is measured (bound + free).

In a low albumin state it is important to consider that the effect of free tacrolimus could be greater than indicated by the reported total level. However this should reach a steady state after 4.5 half-lives of tacrolimus (approximately 2-3 days) as the clearance of unbound tacrolimus will increase to account for this.

Paracetamol
Consider using hepatic dosing of paracetamol 500mg orally (PO) 6-hourly (QDS) in the initial post-transplant period until the graft is functioning appropriately. Intravenous (IV) paracetamol is routinely limited to a maximum three times daily (TDS) frequency for all CUH patients to reduce the risk of therapeutic excess with increased bioavailability of IV compared to PO.

References

Half-life data are taken from the Renal Drug Database* (https://renaldrugdatabase.com/)
The suggested management of drug interactions is taken from Stockley's drug interactions online* (https://www.medicinescomplete.com/)
*except for maribavir (Livtencity®) taken from the manufacturer's SmPC. Awaiting the monograph in Stockley's drug interactions online.

20 Protocols for procedures

20.1 Liver biopsy

No liver biopsy is to be performed without discussion with a consultant hepatologist / transplant surgeon. The biopsy should always be performed by an appropriately trained individual.

All biopsies are performed by radiology under ultrasound guidance.

Criteria for percutaneous biopsy (see BSG Guidelines online and Trust Guidelines on Connect):

- If possible, withhold prophylactic dalteparin the evening before a planned biopsy; ideally Aspirin should be discontinued for 48 hours; and clopidogrel for 7 days; ensure not receiving a direct oral anticoagulant (DOAC) drug.
- For thrombocytopaenia or deranged prothrombin time / INR see separate guidelines for interventional radiology.
- Current group and save to be taken in case transfusion is required.
- Ciprofloxacin prophylaxis 500 mg po stat dose pre biopsy for patients with known cholangiopathy
- Informed, signed consent by individual undertaking the biopsy.
- Warn histology so that technician is available (extension 3177)
- Never undertake more than two passes if you fail to get tissue
- Six-hour bed rest following biopsy and if sign of bleeding call hepatology SpR immediately, secure IV access and resuscitate.
- Contact liver pathologists via phone or email to inform them of post-transplant biopsy in order that biopsy can be processed urgently. Results are usually available the next day.

Transjugular liver biopsies will be requested in specific situations (e.g. marked thrombocytopaenia, coagulopathy, large volume ascites, patients early post transplant, or if pressure studies are required in addition to liver histology). These need to be arranged with Interventional Radiology.

Biopsies at weekends will only be performed in clinically urgent circumstances.

20.1.1 Focal abnormality

Lesions requiring biopsy should be discussed with the radiologist performing the biopsy with all relevant prior imaging because some lesions are more safely biopsied using CT guidance rather than ultrasound.

Preparation

- Consent
- Coagulation studies
- Arrange FFP/platelets if needed (as above)
- Arrange interpreter if the patient cannot understand English

- Sedation is not normally available but if there is no alternative then you will be asked to provide and monitor this during the procedure.

21 Discharges and deaths

21.1 TTOs

Discharge drugs – prescribing tips
Discharge drugs need clinically screening by the transplant pharmacists to ensure the discharge drugs are safely prescribed- this is most important for newly transplanted patients where lack of understanding/experience in managing their medication in the immediate discharge period may lead to confusion and drug errors. Discharge drug writing should be planned so that this occurs when the transplant pharmacists are available Monday-Friday to clinically check the discharges.

Epic limitations to manage
For discharge drugs prescribed in advance of discharge date:

- **Epic does not update the discharge drugs for changes made on the inpatient chart**
- Drugs stopped on the inpatient chart will need to be manually discontinued from the discharge drugs
- Dose changes will need to be updated- e.g. prednisolone, tacrolimus, analgesia
- Drugs newly started on the inpatient chart will appear for reconciliation.

Transplant pharmacy team dispense all immunosuppression + valganciclovir with a label stating ‘Take as directed’ to ensure dosing instructions are correct for numerous dose changes. Therefore it is important that the discharge dosing is correct on the AVS for the patient. Please note that Epic defaults to ‘Take as directed’ for all tacrolimus prescriptions on discharge.

Expected drugs for discharge – newly transplanted patients

Drug	Indication	Comments/considerations
Adoport twice daily	Immunosuppression	• Only prescribe the strengths needed for discharge + 1mg strength needed on first discharge for newly transplanted patients. Each strength needs prescribing separately • Use free-text to enter dosing and frequency, otherwise AVS displays ‘Take as directed’ with an end-date and will drop off the outpatient chart • E.g. **Take Xmg TWICE daily total dose** for each strength • Prescriptions that have completed on the inpatient chart that morning won’t appear for reconciliation.

		• Please prescribe on the discharge, even if further dose adjustments are planned • **Ongoing outpatient supplies from CUH**
Azathioprine or mycophenolate	Immunosuppression	• Add each strength needed. If each strength is not added, it will not be appropriately re-prescribed & dispensed as an outpatient • **Ongoing outpatient supplies from CUH**
Prednisolone	Immunosuppression	• Has dose weaning commenced? • **Ongoing outpatient supplies from CUH**
Aspirin	Anti-platelet	• All patients. Clopidogrel instead if allergy/pre-admission use
Dalteparin	Anti-coagulant	• If indicated. Can BD split dosing change to OD dosing? • Is dosing still appropriate for weight (use Epic dose rounding to available syringe strengths) • Epic defaults to a supply quantity of 1 syringe- change quantity to min 10 days, max 30 days
Co-trimoxazole	PJP prophylaxis	• Duration 3 months total post-transplant
Valganciclovir	CMV prophylaxis	• If indicated. Duration 100 days total post-transplant. • Adjust dosing for renal function • **Ongoing outpatient supplies from CUH**
Nystatin	Topical antifungal	• Until prednisolone dose below 10mg per day
Omeprazole	Gastro-protection	• While prescribed steroids, long-term if indication pre-admission
Oxycodone (other strong opioids)	Analgesia	• Rationalise need for strong opioids prior to discharge- plan to wean & stop where appropriate or switch to lower strength drug e.g. dihydrocodeine, meptazinol • Look at MAR chart/pain report to see regular and PRN break-through usage • Oxycodone liquid- Epic defaults to a 250mg/250ml supply- please **reduce** this quantity as needed • Printed and signed controlled drug forms needed for any discharge dispensing – Epic auto prints for whoever prescribes at discharge (swipe ID badge against printer). • **If strong opioids prescribed at discharge for post-op pain a weaning plan is needed for patient and GP.**

Statin	Cardiac risk	• Restart if taking pre-admission – see interaction table
Colecalciferol Calcium/colecalciferol combined	Vitamin D replacement	• If indicated –level deficient or insufficient. Self-care replacement advised for adequate levels.

21.1.1 Discharge letters

No patient to be discharged without agreement of Consultant Surgeons and Hepatologists and Transplant Coordinators.

The patient should be given a letter for the GP on discharge, and a summary dictated prior to discharge including all relevant details, including operative details, postoperative details, major complications, discharge medications (**must include brand of tacrolimus or ciclosporin to avoid inadvertent switching as NOT interchangeable**) and details of any further management planned and follow-up arrangements. A date for the follow-up outpatient appointment can be planned through liaison with the liver transplant coordinators in their office or on extension 216672.

21.1.2 Outpatients

The transplant outpatient clinics are on Monday, Wednesday and Thursday mornings. For Nottingham and Southampton patients, there may be the option that they are seen in those centres.

Appointments are made via the transplant admin team in conjunction with the clinical team.

Many appointments are now conducted remotely via telephone or video call with the option for F2F review where required.

Patient is reviewed by a member of the transplant clinical team.

If the patient is having a remote review blood tests are required either by local phlebotomy services or via the remote ‘blue box’ system to allow clinical review in the context of up-to-date blood tests.

For distant referring Liver Units separate policies are in place for early follow-up to avoid travelling, but patient preference is also important.

Please ensure patient immunosuppression and valganciclovir supplies are checked in clinic and resupplied if needed as these are not provided by the GP and have to be dispensed from the hospital.

21.1.3 Deaths

If a patient dies on the ward the hepatology consultant, the surgeon on call, and the surgeon who did the operation should all be informed at the earliest opportunity.

The cause of death for patients who die in hospital is discussed and agreed with one of the hospital Medical Examiners. The Medical Examiners are well-placed to advise whether further liaison with the coroner is required.

In the event of a patient dying under circumstances when the death does not need reporting to the coroner, discuss post-mortem examination.

The general practitioner and referring physician should be informed of the patient's death promptly (within 24 hours) and a full summary written – responsibility of the SpR and consultant.

22 The transplant HDU bed admission policy

All admissions must be cleared with the on-call surgical transplant consultant.

The following patients are eligible for admission, in order of priority:

1. Transplant patients
2. Other patients with kidney and liver disease related to transplantation
3. Other patients with kidney/ liver disease – patients in this group should not be admitted to the last bed.

The day-to-day management of the patient is the responsibility of the unit STs. Discharges from the unit are the responsibility of the Consultant and patients cannot therefore be discharged without prior consultation.

23 Monitoring compliance with and the effectiveness of the protocol

The transplant team meets monthly for audit meetings where protocol amendments are discussed based on individual case issues and specific themed audits. The protocol will also be subject to thorough review on an annual basis.

24 Associated documents

- Management of risks associated with infection prevention and control (IPC) strategy
- HCV positive donor protocol (see Merlin)
- CMV protocol (see Merlin)

24.1 Equality and diversity statement

This document complies with the Cambridge University Hospitals NHS Foundation Trust service equality and diversity statement.

24.2 Disclaimer

It is your responsibility to check against the electronic library that this printed out copy is the most recent issue of this document.

24.3 Document management

Approved by:	Transplant Management Board Mr Neil Russell, Transplant Surgery Lead		
Owning department:	Transplant Surgery		
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25 Appendix: Cardiovascular evaluation of potential liver recipients

Background

- This paper proposes revisions to previous guidance dated 2008 and 2014
- The approach from 2008 – 2014 was points-based, proceeding to stress-testing in candidates with multiple risk factors. In 2014, this system was replaced by case-by-case clinical assessment after an audit of early post-transplant cardiac morbidity demonstrated a very low incidence of major adverse cardiac events (MACE), poor test performance, and few if any instances of altered management.
- Relatively few angiograms and only one PCI procedure have been performed in Cambridge transplant candidates in the past 20+ years. A follow-up audit of 90-day cardiovascular outcomes 2000-2020 has confirmed the above findings.
- Age and co-morbidities are increasing in patients presenting for liver transplantation, as has the prevalence of MASH, potentially an independent risk factor for adverse short- and long-term MACE.
- Clinical IHD (history or symptoms) is associated with poorer outcomes after liver transplantation than is seen in recipients without this history. However, in most the added risk does not breach the accepted benchmark of 50% five-year survival.
- 'Silent' IHD is common in liver transplant candidates, but outcomes are clearly better than in those with a clinical history.
- Published data on cardiovascular evaluation before liver transplantation is limited, with small numbers and no randomised trials.
- Since randomised trials in major vascular surgery and in patients with inducible ischaemia in the setting of chronic IHD have not shown survival benefit from prophylactic revascularisation, the rationale for stress-testing leading to angiography and PCI in the context of liver transplantation is open to question.

Current international practice and guidelines

- Consensus guidelines (ACC/AHA 2007, 2014) relating to other types of major non-cardiac surgery have moved away from stress imaging and revascularisation in patients without history or symptoms of IHD.
- However, expert opinion endorsed by ACC/AHA in 2012 acknowledged that stress testing is an acceptable approach in liver transplant candidates with multiple risk factors, despite a lack of supporting evidence. Therefore, most US liver transplant centres have long required stress testing, followed by coronary angiography in patients with known IHD or a positive non-invasive test.

- However, the sensitivity and specificity of DSE and MPI in detecting obstructive coronary disease in this setting are now known to be poor, leading many units to protocolise invasive angiography on the following criteria, affecting >60-70% of current transplant candidates:

    - Known IHD
    - Age >50 with one or more risk factors
    - Age <50 with three risk factors
    - Risk factors include MASH, diabetes, hypertension, renal insufficiency, smoking, strong FH, cerebrovascular and peripheral vascular disease

- In these centres, cardiologists will place one or more stents for perioperative prophylaxis, if feasible and indicated by fractional flow reserve below 0.7-0.8, regardless of the patient's clinical history.

- Outside the US, however, many cardiologists decline intervention in the absence of symptoms, citing ACC/AHA 2014 guidelines and RCTs in major vascular surgery indicating no benefit.

- Newer modalities including CT coronary angiography, MR angiography and perfusion stress-echocardiography have been advocated, but no diagnostic RCT in liver transplantation, major vascular or abdominal surgery has yet been done.

Proposed Cambridge Transplant Unit guideline

1. Careful history to identify potential IHD symptoms (angina, disproportionate exertional dyspnoea, syncope, palpitations)

2. Routine ECG and transthoracic echocardiography

3. Echocardiography should include the following, which must be specified for all external studies:

    a. Quantitative estimation of LV ejection fraction, noting that EF <60% the setting of end-stage liver disease is an independent predictor of MACE and reduced survival.

    b. Assessment for raised left ventricular filling pressure (on 2016 ASE/EACI and current BSE criteria).
    c. Assessment for raised RV systolic pressure, quantifying probability of pulmonary hypertension as low, intermediate or high (on 2016 ASE/EACI and 2018 BSE criteria).

    d. Assessment of RV function, to include *fractional area change* when probability of pulmonary hypertension is intermediate or high, or if any suggestion of RV impairment (2020 BSE criteria)

4. Consult cardiologist if:

a. IHD history when management not optimised.

b. IHD symptoms, aiming is to confirm diagnosis and optimise secondary prevention.

c. LV or RV dysfunction on echocardiogram:

i. to confirm echocardiographer's findings since either may contraindicate transplant

ii. to establish diagnosis and appropriate long-term treatment and follow-up.

d. Clinically significant dysrhythmia (e.g. refractory uncontrolled AF, symptomatic or high-risk heart block, sustained junctional rhythm, etc).

e. Mean aortic gradient >30 mmHg, or other significant valvular / LVOT obstruction: stress testing may be indicated to assess haemodynamic significance.

f. High echocardiographic probability of pulmonary hypertension: requires RHC, which may be performed at referring hospital (see 6. below)

5. Further testing may be indicated if:

a. Suspected but unconfirmed symptomatic IHD, e.g. angina, pre-syncope, disproportionate dyspnoea: CTCA is usual first choice; MPI or DSE if unsuitable for CTCA.

b. High aggregate risk: multiple cardiac AND other risk factors that combine to make the candidate a very poor but not clearly prohibitive perioperative risk. Additional testing should not be done unless the patient is considered an acceptable risk in all other respects. CTCA is usual first choice:

i. If CTCA shows high-risk obstructive disease (>50% LM, >70% proximal LAD, or three-vessel stenoses) transplant perioperative risk is prohibitive.

ii. If patient is unsuitable for CTCA (AF/tachycardia, significant renal impairment, heavy calcification, intolerant of position), MPI or DSE may be considered.

iii. Incremental risk associated with inducible ischaemia would be considered prohibitive without requiring coronary angiography. A negative test would allow transplant.

c. If echocardiogram suggests high probability of pulmonary hypertension or shows any evidence of RV dysfunction (reduced *fractional area change)*, referral for RHC is required. This is to differentiate pulmonary arterial hypertension ('true' portopulmonary hypertension) from pulmonary venous hypertension caused by fluid overload or HFNEF, since these three

conditions have different treatments and prognoses.

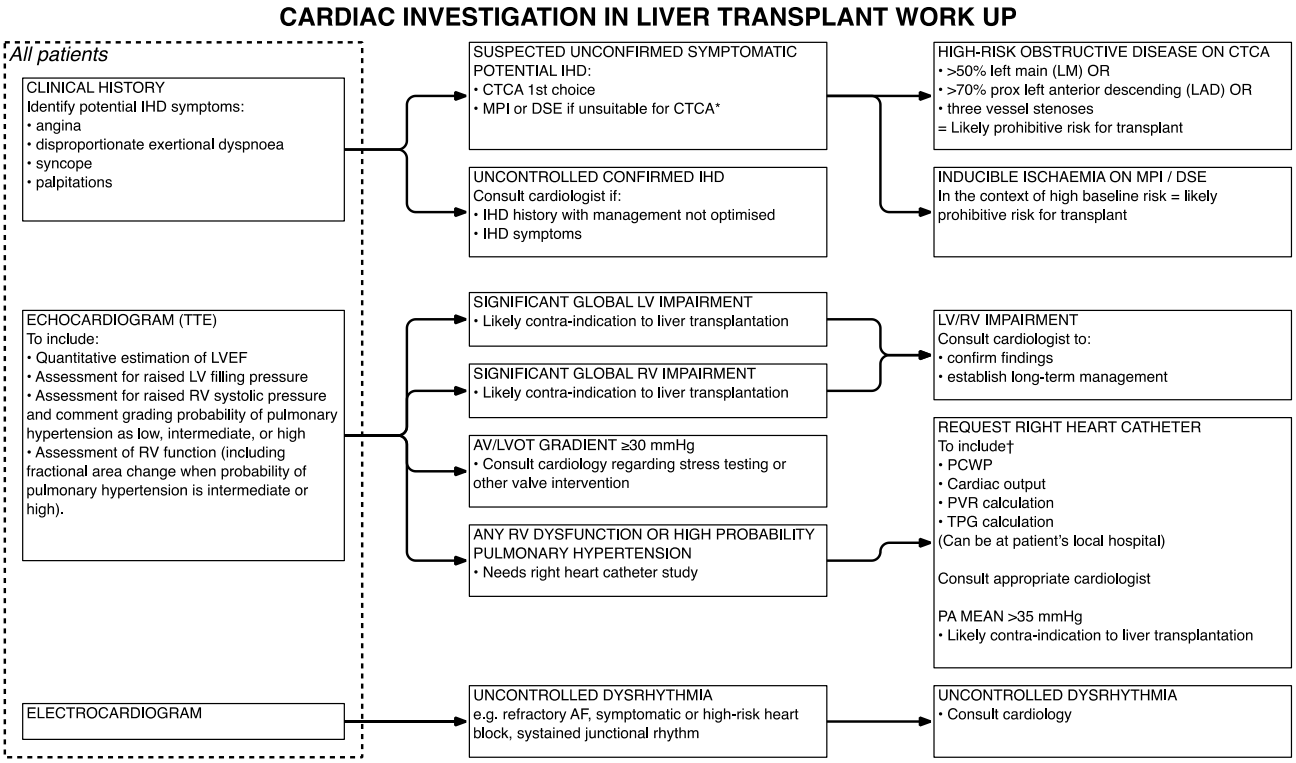
RHC should include measurement of PCWP and cardiac output, and calculation of pulmonary vascular resistance (PVR) and transpulmonary gradient (TPG). Cardiac output is vital in determining diagnosis, management and prognosis. Left heart catheterisation, allowing measurement of diastolic pressure gradient (DPG), is sometimes needed if the cause of pulmonary hypertension remains uncertain.

d. Aortic stenosis and hypertrophic LV outflow tract obstruction: when estimated mean gradient is >30, stress testing may be indicated to assess haemodynamic significance – consult cardiologist.

e. Testing outside these criteria should be discussed with cardiology team

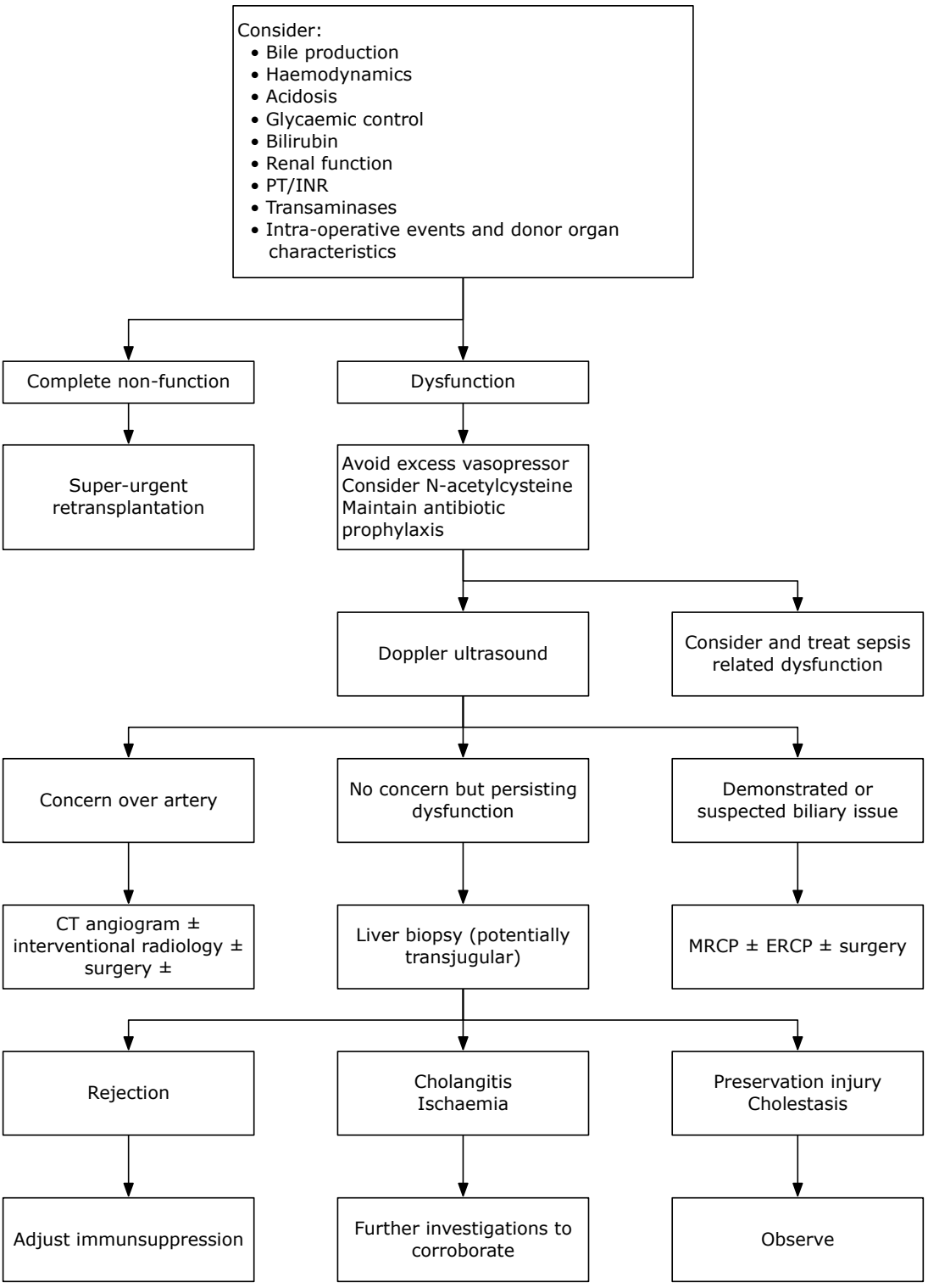
6. Significant global LV or RV dysfunction, or PA mean >35 mmHg normally contraindicate liver transplantation, although this may be reconsidered after treatment.

26 Appendix: Cardiovascular investigation flowsheet

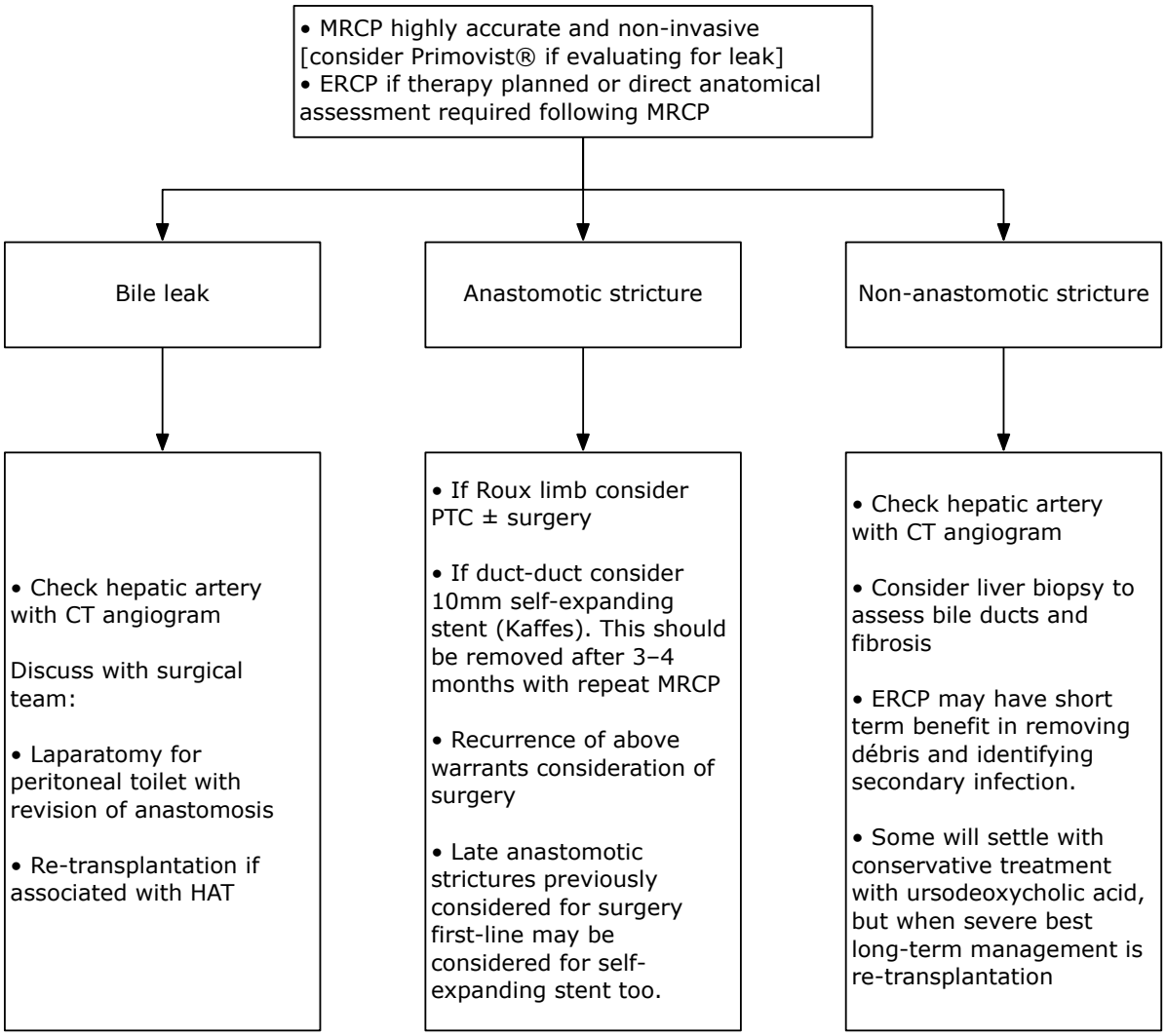


AV = aortic valve; CTCA = CT coronary angiogram; DSE = dobutamin stress echocardiogram; IHD = ischaemic heart disease; LVEF = left ventricular ejection fraction; LVOT = Left ventricular outflow tract; PA = pulmonary artery; RHC = right heart catheterisation; TTE = transthoracic echocardiogram; * CTCA may be unsuitable in uncontrolled tachycardia, significant renal impairment, heavy calcification, position intolerance; † RHC should include measurement of pulmonary capillary wedge pressure (PCWP), cardiac output, and calculations of pulmonary vascular resiststance (PVR) and transpulmonary gradient (TPG)

27 Appendix: Management algorithm of early graft dysfunction



28 Appendix: Management algorithm of biliary complications



29 Appendix: Mycophenolate mofetil and pregnancy-prevention

The following is taken from

https://www.gov.uk/drug-safety-update/mycophenolate-mofetil-mycophenolic-acid-new-pregnancy-prevention-advice-for-women-and-men (accessed 2020-11-29)

Key updated safety advice for healthcare professionals:

- Mycophenolate mofetil or mycophenolic acid should not be used in pregnancy unless there is no suitable alternative treatment to prevent transplant rejection
- Physicians should ensure that women and men taking mycophenolate mofetil and mycophenolic acid understand: the risk of harm to a baby; the need for effective contraception; the need to plan for pregnancy and change treatment as necessary; and the need to immediately consult a physician if there is a possibility of pregnancy
- Mycophenolate mofetil or mycophenolic acid treatment should only be initiated in women of child bearing potential when there is a negative pregnancy test result to rule out unintended use in pregnancy
- Mycophenolate mofetil or mycophenolic acid should only be given to women of childbearing potential who are using highly effective contraception
- Women should use at least one form of effective contraception during treatment and for 6 weeks after stopping treatment, two forms are preferred but no longer mandatory.
- Men (including those who have had a vasectomy) should use condoms during treatment and for at least 90 days after stopping treatment. This advice is a precautionary measure due to the genotoxicity of these products
- Female partners of male patients treated with mycophenolate mofetil or mycophenolic acid should use highly effective contraception during treatment and for 90 days after the last dose

Transplant recipients are given the following advice from the transplant pharmacy team based on guidance issued in 2016 from the Renal Association and in agreement with the Roy Calne Transplant Unit Director;

Pregnancy following transplantation

Female patients: Some of the tablets that you will be prescribed after a transplant can cause problems in pregnancy. This means that it is really important to use effective contraception after your transplant, and to talk to your doctor early if you are thinking about pregnancy so that they can discuss the options for changing your medications with you.

Valganciclovir – use effective contraception during and for at least 30 days after treatment

Mycophenolate / mycophenolic acid – use at least 1 effective form of contraception during and for 6 weeks after stopping treatment. Two forms of contraception are preferred but no longer mandatory.

Male patients: Some of the medications you may be prescribed after a transplant can affect your sperm, so it is important for male transplant patients and their partners to use effective contraception after transplantation:

Valganciclovir – use a condom during treatment and for 90 days after stopping.

Mycophenolate / mycophenolic acid – although there is a very small chance that this medication could affect sperm, there is no evidence of any harm to children fathered by men taking mycophenolate or mycophenolic acid. Some patients choose to switch to an alternative medication if their partner is intending to get pregnant. However, this risk must be balanced against the increased chance of experiencing rejection if you change medications. For most transplant patients, it is likely to be better to continue to take mycophenolate – discuss with your transplant doctor

30 Appendix: Direct-acting oral anticoagulants in liver transplant patients

Please refer to Trust guidelines at:
http://merlin/Lists/DMSRecords/DispRecordTabsDoc.aspx?ID=19744

In relation to liver transplantation:

- The safety of the DOACs remains unclear in liver transplant recipients.
- Dabigatran is contraindicated in patients on ciclosporin and not recommended with tacrolimus and hence should not be used in transplant recipients.
- Rivaroxaban, edoxaban, and apixaban can be considered for use post liver transplant.
- General prescribing and drug interactions relating to rivaroxaban, edoxaban and apixaban can be found in the trust guidelines.

Interactions of particular significance in liver transplant recipients include:

- **Ciclosporin**[1,2] – ciclosporin is a combined P-gp inhibitor and a moderate CYP3A4 inhibitor and as such is likely to interact with resulting in increased blood levels of apixaban, edoxaban and rivaroxaban.
  - In patients with normal renal function this increase is likely to be moderate and the combination should be used with caution.
  - In patients with severe renal insufficiency (CrCl < 30ml/min), age > 80 yrs, or low body weight (< 60 kg) the combination should be AVOIDED

- **Tacrolimus** and **sirolimus** are unlikely to result in a clinically significant interaction.

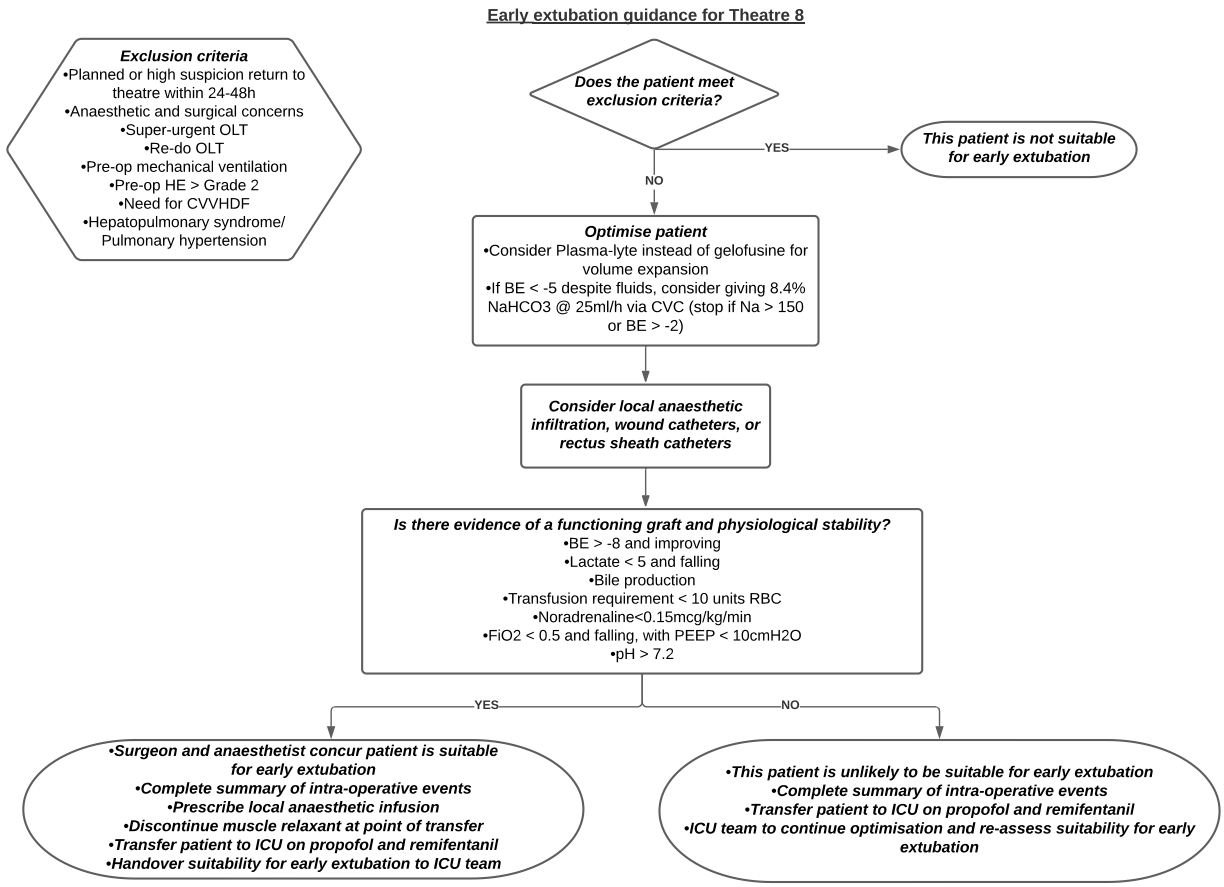
- **Fluconazole**[1] - is a moderate CYP3A4 inhibitor and as such is likely to interact with resulting in increased blood levels of apixaban and rivaroxaban.
  - In patients with normal renal function this increase is likely to be moderate and the combination should be used with caution.
  - In patients with patients with severe renal insufficiency (CrCl < 30ml/min), age > 80 yrs, or low body weight (< 60 kg) the combination should be AVOIDED

Of note, dabigatran, rivaroxaban, edoxaban, and apixaban are contraindicated in patients with liver disease and coagulopathy.

References

1. Hansten PD and Horn JR. The Top 100 Drug Interactions: A Guide to Patient Management, 2014 ed, H&H Publications, Freeland WA 2014.
2. Wannhoff A et al Transplantation. 2014 Jul 27;98(2):Increased levels of rivaroxaban in patients after liver transplantation treated with cyclosporine A

31 Appendix: Early extubation guidance for theatre



32 Appendix: Early extubation guidance for ICU