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## REVIEW

# Adult liver transplantation: UK clinical guideline - part 2: surgery and post-operation

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**ABSTRACT**

Survival rates for patients following liver transplantation exceed 90% at 12 months and approach 70% at 10 years. Part 1 of this guideline has dealt with all aspects of liver transplantation up to the point of placement on the waiting list. Part 2 explains the organ allocation process, organ donation and organ type and how this influences the choice of recipient. After organ allocation, the transplant surgery and the critical early post-operative period are, of necessity, confined to the liver transplant unit. However, patients will eventually return to their referring secondary care centre with a requirement for ongoing supervision. Part 2 of this guideline concerns three key areas of post liver transplantation care for the non-transplant specialist: (1) overseeing immunosuppression, including interactions and adherence; (2) the transplanted organ and how to initiate investigation of organ dysfunction; and (3) careful oversight of other organ systems, including optimising renal function, cardiovascular health and the psychosocial impact. The crucial significance of this holistic approach becomes more obvious as time passes from the transplant, when patients should expect the responsibility for managing the increasing number of non-liver consequences to lie with primary and secondary care.

**INTRODUCTION**

Following successful liver transplant (LT), 12-month patient and graft survival rates in the UK exceed 90% and 80%, respectively.<sup>1</sup> The 10-year survival approaches 70%, and transplant services have an ever-increasing population of long-term survivors.<sup>2</sup> Kidney transplant services

repatriate their transplant recipients to referrers soon after surgery, whereas liver services have historically been more cautious.<sup>3</sup> However, as numbers increase, some aspects of post-operative care are being redistributed to referrers.

Part 2 of this two-part guideline examines:

- Organ donation, organ allocation and organ types.
- LT surgery and post-operative period.
- How immunosuppression should be managed.
- How the patient should be managed post-LT.
- Transplant outcomes.

**ORGAN DONATION, ORGAN ALLOCATION AND ORGAN TYPES****Organ donation**

Figure 1 outlines the source of organs and their relative contributions.<sup>4-6</sup>

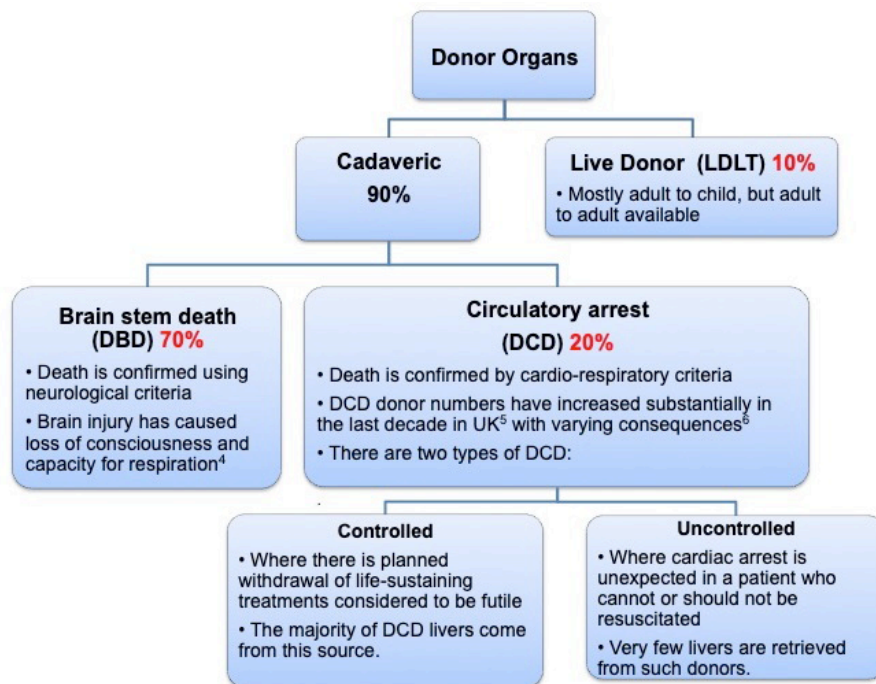
**Organ allocation**

Organ allocation has long been debated across many healthcare systems. Organs can be allocated according to 'need' (sickest first), 'utility' (best use of organ) or 'benefit' (combines need and utility). Most countries have adopted need as the main criterion. The UK recently agreed to use the Transplant Benefit Score (TBS) to allocate donor after brain death (DBD) livers, and it is likely that donor after cardiac death (DCD) livers will follow the same process. TBS contains 21 donor and recipient variables, including donor age, cause of death, body mass index (BMI), diabetes, recipient's indication for transplant, creatinine, sodium, bilirubin,



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**Figure 1** Sources of livers donated for transplantation. DBD, donor after brain death; DCD, donor after cardiac death; LDLT, live donor liver transplantation.

albumin, waiting time, maximum tumour size and number of tumours. The National Liver Offering Scheme ensures a complete de-linking between organ retrieval and allocation.<sup>7</sup> Variant syndromes are allocated livers in proportion to the number on the waiting list.

### Organ types

DCD grafts are usually whole livers but, if of sufficient quality, can be ‘split’ and transplanted into a child *and* adult. Partial grafts carry additional risks,<sup>8</sup> so factors such as donor age, time on the intensive care unit and obesity will aid donor-team decision-making. All grafts risk transmission of malignancy and viruses so donor screening, transmission recognition and reporting facilitate accurate estimation of these risks.<sup>9</sup>

### LIVER TRANSPLANTATION SURGERY AND THE POST-OPERATIVE PERIOD

The recipient’s LT operation commences when the surgeon is assured of donor organ size, quality and anatomy. Hence, some recipients will experience a ‘false start’ if the organ quality is poor; however, if the organ is suitable, surgery will proceed (figure 2 outlines the order of surgery).

Figure 3 and online supplementary appendix 1 outline the post-LT complications. These can be broadly divided into immediate and early complications. Any major abdominal procedure carries a risk of bleeding and infection in the immediate post-operative period. The additional, more specific, surgical complications relate to the

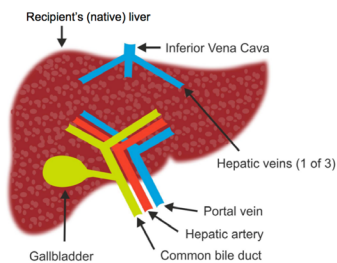
various vessel anastomoses (figure 2), including portal vein thrombosis, hepatic artery thrombosis and biliary leak or stricture. Live donor liver transplant (LDLT) and DCD allograft recipients are more prone to biliary and vascular complications. Hepatic artery stenosis and rare complications such as primary non-function may require re-graft,<sup>10</sup> so all listed recipients are warned of this possibility. Conversely, portal vein thrombosis and biliary complications can usually be managed without the need for further surgery. These ‘immediate’ complications arise in the first few days and hence will all be managed in the liver transplant unit (LTU). Complications arising after the first week or so (see figure 3) include the ever-present risk of hepatic artery thrombosis, the emerging risk of organ rejection and diverse infections, including those related to graft transmission and immunosuppression.

### HOW SHOULD IMMUNOSUPPRESSION BE MANAGED IN THE CLINIC?

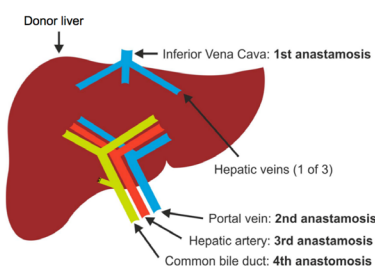
Most LT recipients require lifelong immunosuppression, although some develop ‘operational tolerance’ and can maintain graft health without immunosuppression.<sup>11 12</sup> Maximum immunosuppression is required early post-transplant, when rejection risk is greatest. Frequently used agents are shown in online supplementary appendix 2. The most common regimens include<sup>13</sup>

- ▶ A calcineurin inhibitor (CNI) (usually tacrolimus) with or without corticosteroids.

1. Skin preparation.
2. Skin incision as per surgeon's preference.



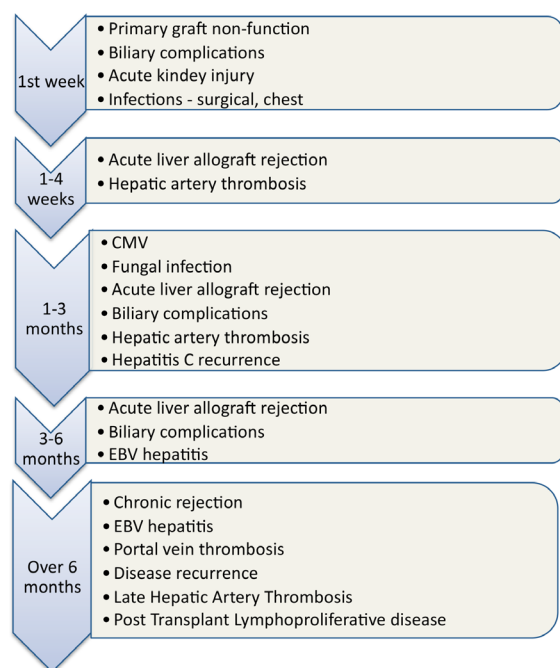
3. Intra-abdominal check to ensure no malignancy, identify undiagnosed anatomical variants and any other anomaly.
4. The patient's own liver is dissected, mobilised and removed, being careful to identify the bile ducts, portal vein, hepatic artery and veins and the inferior vena cava.
5. The new liver is then implanted (having removed the gallbladder) with the vessels being re-attached in the following order:



Each of these anastomoses vary from case to case, according to donor and recipient variant anatomy, recipient diagnosis (e.g. biliary anastomosis in PSC) and surgeon's preference.

6. Closure of the abdomen, once the surgeon is certain that the surgical field is dry.

**Figure 2** Order of liver transplantation surgery. PSC, primary sclerosing cholangitis.



**Figure 3** Post-transplant complications. CMV, cytomegalovirus; EBV, Epstein-Barr virus.

- ▶ A CNI with an antimetabolite (azathioprine or mycophenolate mofetil) with or without corticosteroids.
- ▶ Mycophenolate and corticosteroids.

Immunosuppression is associated with significant side effects, which may be related to immunosuppression itself (such as increased risk of some cancers and infections) or drug-specific side effects (such as steroid-associated osteopenia or CNI-associated renal impairment) as in [table 1](#). Golden rules for managing immunosuppression are outlined below, and the LTU's pharmacist is an additional important resource.

#### Golden rules with immunosuppressants

1. Always use the same brand of CNI and do *not* interchange.
2. CNI and mTOR inhibitor (mTORi) doses should be informed by the use of therapeutic drug monitoring (TDM).
3. Target trough whole blood levels for the stable recipient are usually between 3 and 8 ng/L for tacrolimus and between 80 and 100 µg/L for cyclosporin.
4. For 'trough' CNI drug levels, ensure that the patient has not taken their drug on the morning of the blood test.
5. Always check any new prescriptions for potential drug-drug interactions.
6. The development of side effects does not necessarily equate with over-immunosuppression.

#### Immunosuppression regimens

Immunosuppression regimens vary considerably between units and individuals. The choice of immunosuppressive regimen is dependent on many factors, including

1. Time after transplant. Induction regimens (not included in these guidelines) use antilymphocytes agents and interleukin-2 receptor blockade: with increasing time after transplantation, the immunosuppressive burden can be reduced. Sirolimus (mTORi) is deferred for 3 months as it impairs wound healing and risks hepatic artery thrombosis.<sup>14</sup>
2. Indication for transplant. Many LTUs use long-term corticosteroids in autoimmune conditions,<sup>15</sup> whereas high-dose steroids promote viral replication in active hepatitis C virus (HCV) infection.
3. Acute and/or chronic rejection episodes.
4. History or risk of cancer. mTORi may reduce the risk of some de novo cancers.
5. Complications of previous immunosuppression therapy.
6. Wish of recipient or partner to conceive and/or breast feed (mycophenolate and mTORi are teratogenic).
7. Renal impairment. For those with pre-transplant renal impairment, drug regimens with reduced CNI exposure may be appropriate.
8. Comorbid diseases. Diabetes mellitus or significant osteopenia is exacerbated by steroids. Azathioprine is frequently used in patients with inflammatory bowel disease requiring LT for primary sclerosing cholangitis (PSC).

There are few prospective, large-scale trials comparing different immunosuppressive regimens and these mostly focus on relatively short-term outcomes (<1 year), so the

**Table 1** Major side effects of commonly used immunosuppression

Immunosuppressant	Side effects
Calcineurin inhibitors	Renal impairment Infections (viral, bacterial and fungal) increased risk Hyperuricaemia Gout Hypertension Hypercholesterolaemia Glucose intolerance Hypomagnesaemia Hyperkalaemia Headaches/migraines Insomnia Tremor Hirsutism Gum hypertrophy
Mycophenolate	Diarrhoea Leucopenia Teratogenic (should be avoided by mother prior to and during pregnancy and male patients planning to father children. Men should use condoms during treatment and for at least 90 days after cessation of treatment. Female partners should also use a highly effective method of contraception for this duration.) Infections (viral, bacterial and fungal)
Corticosteroids	Sodium retention Fluid retention Potassium depletion Infections (viral, bacterial and fungal) Hypertension Carbohydrate intolerance and diabetes mellitus Cushingoid facies Growth retardation Menstrual irregularities Ophthalmological issues, for example, cataracts, glaucoma Osteoporosis and increased fracture risk, aseptic necrosis of femoral head Myopathy Muscle weakness Increased bruising Skin thinning/acne Altered mood Headaches Peptic ulceration Pancreatitis
mTORi	Infections (viral, bacterial and fungal) Thrombocytopenia and leucopenia Impaired wound healing Lymphocele Rash Menstrual disorders Interstitial lung disease Hyperlipidaemia Proteinuria Possible increased risk of hepatic artery thrombosis Infections (viral, bacterial and fungal) Hepatotoxicity Bone marrow suppression

mTORi, mTOR inhibitor.

evidence base for immunosuppression is often based on retrospective analysis and clinical experience.

#### Pharmacokinetics and pharmacodynamics of immunosuppressants

TDM is used to adjust the dose of some drugs, especially CNI and mTORi. Usually, trough levels are used to direct therapy with higher target levels in the earlier

post-operative period. TDM 2 hours after ingestion has been advocated for ciclosporin but is rarely used.<sup>16</sup> TDM for mycophenolate has been advocated but is not used in routine practice.<sup>17</sup>

Drug metabolism is affected by many factors, including preparation and formulation, whether the medication is taken with food, co-morbid disease (including replicating HCV), intercurrent infections (especially diarrhoea or vomiting), change in liver function, use of other drugs (including herbal remedies) and genetic factors (such as CYP3A5 isoenzymes for CNI and thiopurine methyltransferase for azathioprine).

There are different preparations of the commonly prescribed agents available and different preparations with different pharmacodynamic profiles. For example, different preparations of tacrolimus are licensed for once daily or twice daily dosing and generic preparations that do not all have bioequivalence. Prolonged-release tacrolimus may be more cost-effective than two times per day release and may be associated with better outcomes.<sup>18</sup> The MHRA has advised that the growing number of oral tacrolimus products available increases the potential for inadvertent switching between products, which has been associated with toxicity and graft rejection.<sup>19</sup> Similar considerations apply to formulations of ciclosporin. Therefore, to ensure maintenance of therapeutic response when a patient is stabilised on a particular brand, oral tacrolimus products should be prescribed and dispensed by brand name only. If a prescriber considers that switching a patient to a different brand of oral tacrolimus would be of benefit, the change requires careful supervision and therapeutic monitoring by an appropriate specialist. There is some evidence that a significant variation in trough levels may be associated with a worse outcome.<sup>20–21</sup> Similarly, mycophenolate sodium and mycophenolate mofetil are not interchangeable.

#### Adherence post LT

The rate of non-adherence to immunosuppression regimes approaches 40% in some studies<sup>22</sup> (although non-adherence definitions are inconsistent across studies). Reasons for non-adherence vary between age groups and include side-effect profiles, perceived harm, changes to physical appearance and psychological distress. At all clinic visits, non-adherence should be considered and discussed with patients and their family, ideally by the specialist pharmacist.<sup>23</sup>

#### HOW SHOULD THE PATIENT BE MANAGED AFTER LT?

Following discharge after LT, patients are reviewed weekly by their LTU. In many LTU's, the surgical team supervises the first 3 months post surgery. Depending on the complexity of surgery, distance to travel and post-operative complications, patients can expect to be

‘weaned off’ their weekly transplant clinic visit as care is increasingly shared with their local hospital (see [box 1](#)).

Post-LT survival has been steadily rising for the last 20 years.<sup>24</sup> Improved surgical expertise, better patient selection and better immunosuppression have contributed, such that *non-liver* causes such as malignancy (22%), cardiovascular disease (11%), infection (9%) and renal failure (6%) are the leading causes of mortality 1 year post surgery.<sup>25</sup> Beyond 12 months, the metabolic syndrome emerges as being of increasing relevance to recipients.

### Graft dysfunction

Most LT recipients return to their referrers outpatients with normal or stable LFTs. Any variance should be investigated thoroughly ([table 2](#)) to include a check of adherence, any new medication and an ultrasound scan (with Doppler). Further investigation of graft dysfunction for infection, rejection and disease recurrence will likely take place at the LTU and are outlined further:

#### Rejection

Rejection should be considered if liver biochemistry deteriorates post-LT. The classification of liver allograft rejection has recently been revised by the Banff Working Group<sup>26</sup> (see online supplementary appendix 3). The most common form is T cell-mediated rejection where symptoms include fever, fatigue, jaundice and liver tenderness, which may occur with a rising transaminase and, possibly, leucocytosis. A biopsy is usually mandatory (see online supplementary appendix 3 for interpretation and management) and should be forwarded to the LTU as accurate interpretation is critical. Antibody-mediated rejection is rare and a detailed discussion is beyond the scope of this review. Chronic rejection (also termed ‘ductopenic’ rejection) typically occurs several months or more post-LT and is potentially reversible, so a liver biopsy with expert interpretation is mandatory.

#### Infection

- ▶ CMV infection usually occurs in a virus-naïve recipient receiving an organ from a previously infected donor. In such instances, the recipient will receive 6 months of oral valgancyclovir as prophylaxis. CMV infection causes fever, fatigue and gastrointestinal symptoms with neutropenia and positive CMV PCR.
- ▶ During the first 6 months post-LT, opportunistic infections such as those caused by *Aspergillus* can appear, and latent infections such as those caused by *Mycobacterium tuberculosis* may be reactivated.
- ▶ Beyond 6 months, immunosuppression is frequently reduced, so infections then align with those seen in the non-immunosuppressed population. In addition, post-LT prophylactic agents such as co-trimoxazole, valgancyclovir and isoniazid usually stop between 3 and

6 months post-LT and should be considered if new infections appear.

- ▶ Chronic hepatitis E is under-recognised and should be considered in *any* LT recipient developing graft dysfunction. A positive hepatitis E PCR may require ribavirin treatment.<sup>27</sup>

#### Disease recurrence

Following LT, disease recurrence frequently occurs:

- ▶ Hepatitis B requires ongoing viral suppression.
- ▶ Untreated hepatitis C requires clearance post LT.
- ▶ Non alcoholic steatohepatitis (NASH) can return, especially if obesity, hypertension, hypercholesterolaemia and diabetes control worsen post-LT.
- ▶ Alcohol-related liver disease—addiction services and open discussion with patient.
- ▶ PBC recurrence is found in up to 50% at 5 years. Ursodeoxycholic acid (URSO) is often used, but there is limited experience with obeticholic acid.
- ▶ PSC recurs in up to 70% at 5 years; there is no effective treatment, although ursodeoxycholic acid (UDCA) is sometimes used.

#### Renal dysfunction

The cumulative incidence of end-stage renal failure (ESRF) post-LT was 4% in Fisher’s series at 10 years,<sup>28</sup> while the frequency of chronic kidney disease at this time, approaches 25%.<sup>29</sup> The longer the follow-up, the more renal dysfunction occurs, and this is associated with substantial cardiovascular mortality and morbidity. Poor pre-operation renal function, along with type 2 diabetes, hypertension and CNIs, are the major determinants of declining post-transplant renal function.<sup>29</sup>

#### Cardiovascular disease

Despite careful evaluation pre-surgery, cardiovascular risk increases post-LT. The proportion of transplant recipients with pre-existing metabolic syndrome is increasing as the population’s median BMI rises.<sup>30</sup> A recent retrospective study from the USA identified a new cardiovascular disease within 8 years of surgery in almost a third of all LT recipients.<sup>31</sup> Significant risk factors included age, diabetes, smoking, hypertension, estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m<sup>2</sup> and prior cardiovascular disease. Careful attention to risk factors and lifestyle is important in all recipients.

#### Post-transplant development of diabetes mellitus

Post-transplant diabetes mellitus (PTDM) increases the risk of infection and cardiovascular events, and decreases graft and recipient survival as well as quality of life (QOL).<sup>32</sup> Risk factors for development of PTDM include HCV infection, male gender, corticosteroid use, pre-LT diabetes and CNI (tacrolimus> ciclosporin).

**Box 1 Management of post liver transplant (LT) patient in the clinic****General**

- ▶ Careful drug history to ensure no new renal toxins have been started.
- ▶ Adherence.
- ▶ Careful blood pressure (BP) monitoring aiming for a systolic BP of <140 mm Hg and a diastolic BP of <85 mm Hg. Home monitoring may be necessary.
- ▶ BMI monitoring, monitoring weight in non-obese and advice on weight reduction in obese patients.

**Abnormal liver function tests (LFT)**

- ▶ Check medications, including herbal remedies.
- ▶ Ultrasound liver for space-occupying lesion and biliary anastomotic stricture, and Doppler of hepatic artery and portal vein for patency.
- ▶ Viral hepatitis screen to include hepatitis A, B, C and E; cytomegalovirus (CMV); and Epstein-Barr virus (EBV).
- ▶ Consider liver biopsy (disease recurrence or rejection).

**Renal dysfunction**

- ▶ Close monitoring is necessary.
- ▶ Mycophenolate mofetil use enables CNI dose reduction.
- ▶ Seek help from multidisciplinary, especially diabetologists and nephrologists.
- ▶ Seek help early as, once lost, renal function tends *not* to recover.

**Cardiovascular disease**

- ▶ Statins are safe and appropriate.
- ▶ Continue CNI but minimise use of statins with cyclosporin, and in patients on sirolimus, carefully monitor lipids.
- ▶ Use of cardiovascular risk scores such as QRISK .

**Post-transplant diabetes**

- ▶ Ensure close control with regular evaluation.
- ▶ Effective management of glucose control.
- ▶ No particular advantage of one antidiabetic drug over another.
- ▶ Rapid minimisation of steroids if safe.

**Hypertension**

- ▶ Careful choice of antihypertensive, always check drug–drug interactions.
- ▶ First line: calcium channel blockers, such as amlodipine, reduce systemic vascular resistance and improve renal blood flow with minimal side effects and no interactions with CNI.
- ▶  $\beta$ -Blockers are safe and widely used.
- ▶ Drugs that block the renin–angiotensin system, such as ACE inhibitors and angiotensin-receptor blockers, are best avoided in the early post-operative period when plasma renin activity is low and can exacerbate the hyperkalaemia seen with CNIs. The renin–angiotensin system does recover later in the post-transplant period, and then these drugs can be useful.
- ▶ Diuretics can damage renal function and are best avoided.

**Dyslipidaemia**

- ▶ Aggressive management is necessary.
- ▶ Dietary interventions have little effect on dyslipidaemia.
- ▶ Long-term corticosteroid use can also contribute to hyperlipidaemia, so attempting to minimise corticosteroid use long-term is appropriate.
- ▶ Sirolimus is associated with high rates of dyslipidaemia.
- ▶ Statins are usually safe, efficacious and well tolerated post-LT.
- ▶ Pravastatin and atorvastatin appear effective, have little significant interactions with CNI and are well tolerated.
- ▶ Hypertriglyceridemia with normal cholesterol levels is also common post-LT.

**Obesity**

- ▶ Advice and education of patient and family on the waiting list *prior* to surgery.
- ▶ *Early* resumption of advice and weight supervision post surgery.
- ▶ Diet education is critical at the early stage, and exercise becomes possible once wounds have healed.
- ▶ Minimise length of steroid use in obese recipients.
- ▶ Place similar emphasis on dangers of weight gain as is placed on the other core issues (including rejection and infection) in the early post-transplant period.
- ▶ All options, including surgical and medical solutions, are possible in the post-LT patient, as per standard protocols.

**Smoking**

- ▶ All patients should be rigorously questioned over tobacco use.

Continued

## Box 1 Continued

- ▶ Patients should be actively and repeatedly encouraged to stop smoking.
- ▶ Use of nicotine patches safe pre-LT and post-LT.
- ▶ Careful education of patients in how to identify early signs of head and neck cancer in this group.

**Osteoporosis**

- ▶ All patients with chronic liver disease should have a bone densitometry scan, regardless of whether they are being assessed for transplantation.
- ▶ Minimise corticosteroid and heparin use and avoid loop diuretics as these drugs promote osteoporosis.
- ▶ Optimise calcium and vitamin D intake.
- ▶ Maintain weight-bearing exercise.
- ▶ Consider repeat bone densitometry scan at 12 months post-transplant.
- ▶ Prevention and treatment should be consistent with national guidance.
- ▶ Note that bisphosphonates are both safe and effective post-transplant.

**Alcohol**

- ▶ Check for alcohol use post-LT.
- ▶ Ensure addiction services are being used, where appropriate.
- ▶ Facilitate honest and open discussions with patient and family over alcohol, drug and tobacco use.

**Cancer**

- ▶ Transplant recipients should avoid sun exposure, wear a hat and use factor 50 sunscreen.
- ▶ Patients should participate in national screening programmes (cervical, breast and bowel).
- ▶ Patients must be told to seek urgent dermatological opinion if skin changes are noticed, and every recipient should have a total skin review (head to toe) annually, to look for moles, basal cell carcinoma and other skin tumours (annual 'MOT').
- ▶ Specific questions on smoking should be asked at every clinic review and appropriate advice provided.

**Post-transplant systemic hypertension**

Pre-LT, arterial hypertension is rare, but most recipients develop hypertension following LT.<sup>33</sup> Corticosteroids and CNIs are largely responsible.<sup>34</sup>

**Post-transplant development of dyslipidaemia**

Patients requiring lipid-lowering agents pre-LT should continue after surgery. Advanced liver disease lowers cholesterol levels because of impaired hepatic synthesis and esterification; however, patients with cholestatic liver disease may have high serum cholesterol levels if the liver synthetic function is preserved.<sup>35</sup> Hyperlipidaemia is more frequent with ciclosporin than tacrolimus.<sup>36</sup>

**Obesity**

Obesity occurs in almost half of LT recipients in some series.<sup>37</sup> Virtually all of those obese pretransplant remain so, and in those who were normal weight pre-LT, a third will become obese. Important factors include improved appetite and corticosteroid use, coupled with the reversal of cirrhosis, effectively

removing the associated catabolic state. The cardiovascular mortality and morbidity rise, along with renal disease and non alcoholic fatty liver disease (NAFLD), in the recipient's graft.<sup>38</sup>

**Post-transplant smoking**

Up to a quarter of patients in centres around the world will be regularly smoking tobacco at the time of their LT.<sup>39</sup> While the European Association for the Study of the Liver (EASL) recommends abstinence before listing, UK transplant centres do not take an 'absolutist' view.<sup>40</sup> Cigarette smoking promotes fibrosis in hepatitis C, PBC and alcohol-related liver disease (ArLD) and probably increases the likelihood of hepatoma developing. The data on graft and recipient survival are conflicting with respect to tobacco smoking, but cardiovascular disease is certainly more prevalent.<sup>41</sup>

**Osteoporosis**

Inadequate bone density is very common in the end-stage liver disease population.<sup>42</sup> More advanced chronic liver disease and cholestatic liver diseases are associated with more advanced bone loss. Within the first 12 months after LT, bone density rapidly deteriorates, predisposing to fractures.<sup>43</sup>

**Post-transplant alcohol use and misuse**

All LT candidates are questioned over alcohol use, regardless of indication. Depending on definitions used, up to a quarter of patients transplanted for ArLD return to potential harmful consumption levels, and

**Table 2** Cause of graft dysfunction following liver transplantation

**Causes of abnormal liver function tests (LFT) post-transplant**

Parenchymal	Rejection, infection or disease recurrence
Drugs	Antibiotics or immunosuppression
Biliary	Stricture, leak or stones
Malignancy	Primary or secondary

LFT, Liver Function Test.



**Table 3** Patient survival times post liver transplant, depending on age of recipient (source eltr.org<sup>24</sup>)

Age of recipient (years)	1-year survival (%)	5-year survival (%)	10-year survival (%)	20-year survival (%)
18–45	84	75	66	50
46–60	83	70	59	36
60–70	80	65	49	21

twice that many will return to some sort of alcohol use.<sup>44 45</sup> When significant relapse occurs after LT, the rate of graft damage rises, as does mortality.

For patients transplanted for non-ArLD indications, standard advice to maintain alcohol intake below 14 units/week is appropriate.

### Cancer

The risk of malignancy, particularly skin cancers and lymphoma, rises in LT recipients.<sup>46</sup> Cancer of the lung, head, neck and colon are more common, whereas prostate and breast cancers have a similar prevalence to age-matched and sex-matched controls.

Post-transplant lymphoproliferative disorder is usually EBV driven and usually occurs in the first 12 months post-LT. While classical symptoms of fever, night sweats and weight loss are seen, they can sometimes be more subtle. Therapy is initiated by reducing immunosuppression combined with standard chemotherapy techniques.

Online supplementary appendix 4 displays a specimen outpatient proforma.

### OUTCOMES OF LT

This section examines patient (table 3) and organ (table 4) survival, as well as other outcome parameters, such as QOL, return to employment and psychosexual outcomes.

#### Patient outcomes

Patient survival times (table 3) reported in the European Liver Transplant Registry (ELTR) show that survival depends on the indication and the age of the recipient. However, there is a cohort effect, and long-term patient and graft survival has been steadily improving over the last 20 years.

**Table 4** Graft survival over time for first transplant, second transplant and third transplant (source eltr.org<sup>24</sup>)

Graft number	1-year survival (%)	5-year survival (%)	10-year survival (%)	20-year survival (%)
First	79	66	55	36
Second	58	46	36	22
Third	53	42	33	27

#### Graft outcomes

Graft survival times (table 4) reported in the ELTR demonstrate that re-grafts do not last as long as the first organ transplanted.

#### Psychosocial outcomes following LT

##### Quality of life

Assessing successful outcomes following LT has historically focused on survival rates for both the patient and graft. More recently, with ever improving 'hard' outcomes, it is becoming recognised that measures of a successful LT should include aspects of Quality of Life (QOL).<sup>47 48</sup> Evaluation of outcomes according to QOL following LT are limited due to the lack of a standardised framework for evaluation and data collection; the generic health assessment questionnaires are the most widely published (Short Form 36 and the Hospital Anxiety and Depression Score) but are limited by their lack of disease-specific elements.<sup>49</sup>

Generic health-related quality of life (HR-QOL) improves following LT, and improvements are similar to outcomes in kidney, heart and lung transplant recipients; however, HR-QOL scores fail to return to that of sex-matched and age-matched healthy individuals.<sup>50</sup> Improvements are most marked in the first 2 years following LT, with positive changes in psychological, physical, social, personal and overall health perceptions.<sup>51</sup> Assessment of anxiety and depression, specifically, shows a decline in the longer term, reported for 2 years after LT, secondary to concerns regarding disease recurrence and accrument of comorbidities accentuated by immunosuppression use. Conversely, improvements in physical functioning and overall life satisfaction scores appear more sustained over time.<sup>51</sup>

##### Employment

LT recipients who return to work have a significantly better QOL compared with those who are unemployed. The percentage of recipients who return to work varies from 26% to 57% and is dependent on time from LT and disease aetiology.<sup>52 53</sup>

##### Sexual function and pregnancy

Sexual function and fertility improves following LT but does not reach that of healthy age-matched and sex-matched individuals with reports of decreased libido, difficulty in reaching orgasm, erectile dysfunction and reduced satisfaction.<sup>54–56</sup> For men, erectile dysfunction usually improves post-LT but remains in some due to a combination of medication, comorbidities and depression.<sup>56 57</sup> Sexual health in women has been less well studied; however, dysfunction following LT correlates with a reduction in QOL.<sup>56</sup> Fertility can return as early as 1 month post-LT. Fertility should be discussed with all women of childbearing age following

transplantation; pre-conception counselling and multidisciplinary management of the pregnancy will result in the best possible outcome. Pregnancy should be avoided for the first post-LT year due to its association with acute cellular rejection.<sup>58 59</sup> Pregnancy following LT is associated with a live birth rate of 70% but with an increased risk of foetal loss, prematurity and low birth weight whilst the mother is more likely to develop hypertension, pre-eclampsia, gestational diabetes and graft dysfunction.<sup>58 59</sup> Immunosuppression should be continued throughout pregnancy with the exception of mycophenolate or sirolimus/everolimus, which are teratogenic.

#### Physical activity and diet post-LT

After LT, functional capacity improves, although exercise capacity remains lower than that of age-matched controls.<sup>60</sup> Only 25% of recipients are physically active after LT, and more than two-thirds consume more than the recommended calorie intake.<sup>61</sup> Data to support benefit in targeted exercise/nutritional programmes post-LT are emerging, although these have yet to demonstrate an impact on metabolic syndrome and cardiovascular morbidity and mortality.<sup>62</sup> Obesity is a growing problem, with >30% being obese at 3 years, with older age at transplant and transplant for chronic as opposed to acute liver failure being risk factors.

## CONCLUSIONS

- ▶ Liver transplantation improves the quantity and quality of life of patients with advanced liver disease.
- ▶ The number of organs available for liver transplantation has steadily increased over recent years and is associated with increasing numbers of long-term survivors.
- ▶ After the first year, most patients will be cared for primarily by their local gastroenterologist/hepatologist.
- ▶ Immunosuppression requires careful management to maximise protection from the immune system while minimising harm to other organs.
- ▶ Early post-transplant complications include technical, infection and immunological issues.
- ▶ With time, complications related to the metabolic syndrome and associated cardiovascular risks become increasingly prevalent.

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and acquisition of data for inclusion in the guideline, along with evaluation of relevance to the project; final manuscript editing and approval. SM: consultant transplant hepatologist; coauthored the section on 'how to manage the patient on the waiting list'; brought together the coordinators' input with the transplant centre and the interaction with secondary care referring centre; provided insights from both sides of the secondary/tertiary care interaction and then edited the initial contribution of the section to a more manageable section; ensured relevance of the data collected for the project along with final manuscript editing and approval. KM: consultant transplant surgeon; contributed to the section in part 2 on transplant surgery and outcomes; also provided input in part 1 in the section on transplant assessment and previous surgery; critical role in the planning and acquisition of data for inclusion in the guideline, along with evaluation of relevance to the project; final manuscript editing and approval. DM: consultant transplant surgeon; co-authored the section on transplant surgery with KM and post-transplant surgical complications; also provided input in part 1 in the section on transplant assessment and previous surgery; critical role in the planning and acquisition of data for inclusion in guideline, along with evaluation of relevance to the project; final manuscript editing and approval. JN: consultant transplant hepatologist; wrote the section on post-transplant Immunosuppression with the aid of AC; also contributed to part 1 in an editorial role, when he helped with the original concept; provided a critical role following the original guideline production and prior to its splitting into two halves (parts 1 and 2) and ensuring correct focus was maintained when the manuscript was reduced in size. RP: consultant transplant surgeon; wrote the section on organ allocation and donation; also made a significant contribution to the postoperative care and complications sections and the preop evaluation (part 1); critical role in the planning and acquisition of data for inclusion in the guideline, along with evaluation of relevance to the project; final manuscript editing and approval. AP: liver pharmacist; contributed to part 2, immunosuppression section, but also gave useful input into parts 1 and 2 from the point of view of medication and drug interactions, particularly with viral hepatitis treatment; critical role in evaluating data for inclusion in the guideline, along with maintaining relevance to the project; final manuscript editing and approval. WP: consultant in palliative care; authored the section on palliative care and transplantation in part 1; contributed in part 2 via proofreading and providing critical input; critical role in the planning and acquisition of data for inclusion in the guideline, along with evaluation of relevance to the project; final manuscript editing and approval. LS: transplant coordinator; contributed to the section on how to refer a patient for liver transplant (part 1) and gave input into the section on organ allocation (part 2); critical role in the planning and acquisition of data for inclusion in the guideline, along with evaluation of relevance to the project; final manuscript editing and approval. KS: consultant transplant hepatologist; wrote the section on 'when to refer' in part 1, but also gave significant editorial input to the entire project, at the time of the section merge and subsequent division into two halves; critical role in planning and acquisition of data for inclusion into guideline, along with evaluation of relevance to project; final manuscript editing and approval. DTh and RW: consultant transplant hepatologists; coauthored the section on transplant outcomes; provided critical input into part 1 as well, with respect to the referral process; critical role in the planning and acquisition of data for inclusion in guideline, along with evaluation of relevance to the project; final manuscript editing and approval. DTi: consultant transplant hepatologist; coauthored the section on postoperative care and complications (non-surgical); also supported the entire process by helping the lead author with editing sections and discussion of tables and pictures and deciding on section inclusion, data relevance and final manuscript editing and approval.

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