Long-term Care of the Adult Liver Transplant Recipient☆

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While outcomes after liver transplantation have increased over the last two decades, this is primarily as a consequence of a reduction in early deaths and survival of those who survive the first 6 months has not significantly changed. Causes of premature death and graft loss include cardiovascular disease, renal impairment, malignancy and some infections.

As the number of transplant recipients increase, care is being given by primary and secondary care clinicians. Management of the well patient is crucially dependent on careful assessment and where appropriate intervention, especially of cardiovascular risk – such as advice about avoidance of weight gain; management of hypertension, hyperlipidaemia and diabetes; and provision of appropriate lifestyle advice. Other interventions include surveillance for *de novo* malignancies, active management of immunosuppressive regimen with the need to tailor immunosuppression to the individual. Prompt investigation of abnormalities of liver function is essential. Immune-mediated graft damage still occurs but is less common as a cause for graft loss. Adherence is sometimes an issue, especially in teenagers and young adults, and should be considered and support given where needed. Immunisations (avoiding live and attenuated vaccines) should be encouraged.

Recurrence of disease remains an issue, and some interventions (such as appropriate use of antiviral therapy for those grafted with viral hepatitis, use of ursodeoxycholic acid for those grafted for primary biliary cholangitis or long-term steroids for those grafted for autoimmune disease) may improve and maintain graft function.

Close collaboration between recipient and the attending clinicians in primary, secondary and tertiary care and close attention to modifiable conditions will lead to improved outcomes. (J Clin Exp Hepatol 2022;12:1547–1556)

Liver transplantation has now become an accepted and successful treatment for people with end-stage liver disease. The number of transplants done each year is, with the exception of the last 2 years, increasing and survival improving. Consequently, the number of living recipients is increasing almost exponentially. Thus, in the USA, as of 30 June 2016, 79,188 liver transplant recipients were alive with a functioning graft, including 68,970 who underwent liver transplant as adults; 2 years later, there were 88,715 liver transplant recipients were alive with a functioning graft, including 77,626 who underwent liver transplant as adults.[1] This increase in the number of living liver allograft recipients is starting to overwhelm the capacity of many transplant units to follow up their patients as well as maintain the routine assessments, management on the waiting list and actual transplantation of new patients. As a consequence, more care of the well liver allograft recipient is devolved into primary care and non-specialist transplant units.

Current registry data suggest that the outcome after liver transplantation is increasing year on year, despite the increasing use of higher risk grafts. This welcome increase is a consequence of many factors, including better assessment and management of the graft, better surgical, anaesthetic and microbiology care and improved use of immunosuppression and other drugs. However, this improvement in survival is largely due to a reduced mortality in the first few months (see Figure 1); the outcome of those who survive 1 year has shown, at best, only a marginal improvement.[2]

The cause of death after 1 year was analysed by Watt and colleagues[3]; they analysed the NIDDK LT Database of 798 transplant recipients from 1990 to 1994 (follow up to 2003). Of the 327 recipients who died, causes of death >1 year were hepatic (28%), malignancy (22%), cardiovascular

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Abbreviations: CMV: Cytomegalovirus; CNI: Calcineurin inhibitor; DRR-4i: dipeptidyl peptidase-4 inhibitor; HCC: Hepatocellular carcinoma; HBIG: Hepatitis B Immunoglobulin; HBV: Hepatitis B Virus; HCV: Hepatitis C virus; GLP 1RA: glucagon-like peptide-1 receptor agonists; LDL-C: Low-density lipoprotein cholesterol; LT: Liver transplant; MDRD: Modification of Diet in Renal Disease; MRC: Magnetic resonance cholangiography; mRNA: messenger Ribonucleic acid; mTORi: mammalian Target of rapamycin inhibitor; NAFLD: Non-alcoholic fatty liver disease; NIDDK: National Institute of Diabetes and Digestive and Kidney Diseases; NODAT: New onset diabetes after transplant; NUC: Nucleos(t)ide analogues; PBC: Primary Biliary Cholangitis; PSC: Primary Sclerosing Cholangitis; SGLT2i: sodium–glucose cotransporter 2 inhibitors; SRTR: Scientific Registry of Transplant Recipients; TMPT: Thiopurine S-methyltransferase; USA: United States of America

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(11%), infection (9%) and renal failure (6%). Univariate risk factors for death after 1 year on univariate analysis included male gender, age/decade, pre- and post-transplant diabetes, post-transplant hypertension, post-LT renal insufficiency, re-transplantation after 1 year, pre-transplant malignancy, alcohol-related and metabolic liver disease. Similar risks were found for death after 5 years. Hepatitis C, re-transplantation, post-transplant diabetes, hypertension and renal insufficiency were significant risk factors for liver-related death. Cardiac deaths were associated with age, male gender, alcohol-related and cryptogenic liver disease, pre-transplant hypertension and post-transplant renal insufficiency.

In a more recent study of the SRTR data base, Daniel[4] reported that one fifths of the patients died after the first year after liver transplant. Between 2 and 5 years after transplant, the causes of mortality were malignancy (20%), hepatic causes (16%), infection (13%), coronary heart disease (10%) and the remained due to multi-organ failure, haemorrhage, unknown causes and other reasons. Major causes of deaths after the fifth year posttransplant were 14% due to malignancy followed by coronary artery disease (13%) and infection (11%). Within the Wisconsin programme, the major causes of death more than 5 years after transplant were malignancy (22%), coronary artery disease (16%), infection (14%) and hepatic problems (5%). Most of the malignancies were *de novo* disease, especially lung cancer (26%), lymphoproliferative disorders (14%), colorectal cancers (12%) and head and neck cancers (9%). Comparable findings come from other studies; thus, in a small study from Turkey, Egeli and colleagues found that the main causes of late mortality in liver transplant are malignancy, recurrence of hepatitis C, infection, coronary artery disease, graft rejection and biliary complications.[5] The implications from these and similar studies are shown in Table 1. Graft loss, from late technical causes or immune mediated damage, is an important cause of graft loss and reduced patient survival but plays a small role, largely because health care professionals have become adept at managing immunosuppression. Improvement in survival after liver transplant is therefore dependent on treating the modifiable causes of premature death,[6] and some aspects of this will be discussed.

MANAGEMENT OF THE LONG-TERM LIVER ALLOGRAFT RECIPIENT

The majority of liver allograft recipients are well, and their management is not complex and can usually be effectively managed by a primary care physician or non-specialist hospital clinician. The key factor is good management is close attention to detail and early intervention when needed. Close collaboration with the Transplant Centre is essential; this is necessary so that any complication can be quickly recognised, and treatment instituted. As experience increases, new information becomes available and new

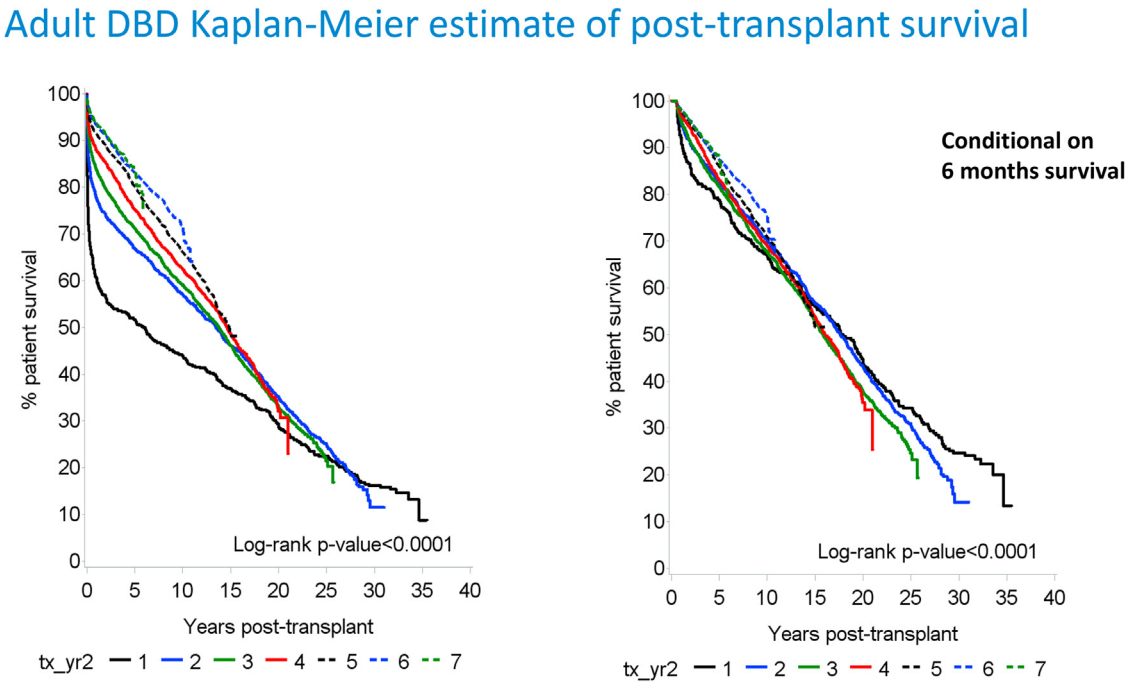

Figure 1 Survival of primary adult non-urgent liver allograft recipients of donors with a graft from donation after brain death in the UK by year of transplant (Tx_y2); (data courtesy of Sue Madden, NHS Blood and Transplant. (Tx_y2 1: 1985-89, 2 1990-1994, 3 1995-1999, 4 2000-04, 5 2005-09, 6 2010-14, 7 2015-17).

Table 1 Long-term Survival of Liver Transplant Recipients.

Survival of those who have lived more than 1 year has not improved	
Graft loss is an uncommon cause of reduced patient survival	
Main causes of reduced graft survival include	Coronary heart disease *De novo* malignancy Infection
Risk factors for premature death include	Renal failure Diabetes Hyperlipidaemia Obesity

Table 2 Assessment of the Well Adult Liver Transplant Recipient.

History	General Health – physical and mental Smoking history Alcohol use Illicit drug use
Immunosuppression	Drugs and dose
Other medications	Prescribed Over the counter Natural remedies and supplements
Compliance	
Physical activity Immunisation status	
Examination	Weight Blood pressure
Blood tests	Full blood count, liver and renal tests blood sugar blood lipids therapeutic blood monitoring
Urine tests Monitoring as required	Albumin/proteinuria Bone health Disease recurrence Cancer screening

treatments being introduced and changes in 'routine' management become advisable. Furthermore, transplant centres need to retain their registries.

In the author's view, the assessment of a well liver transplant recipient is helped by a simple tick box exercise,[6] and the questions and data required are shown in Table 2. The key point about optimal management of the liver allograft recipient is to ensure all relevant information is collated and any abnormal symptoms, findings or results investigated and, where appropriate, treatment instigated. Prompt referral to the specialist transplant clinician is necessary when abnormalities in the graft are suspected or noted or when a change in immunosuppression is indicated.

Standard liver tests are a useful guide to the status of the graft, but it must be remembered that graft abnormalities may be seen in the presence of normal liver tests, normal graft function may be seen with abnormal liver tests and liver histology is usually required to investigate the cause and significance of abnormal liver tests. In particular, rejection cannot reliably be diagnosed without histology.

There are many factors that contribute to the increased cardiovascular morbidity seen after liver transplantation,[7] and these include obesity, hypertension, renal impairment, medication and diabetes mellitus. These factors must be managed appropriately, and guidelines are given below.

Diabetes: Diabetes may pre-exist liver transplant or may develop in the post-transplant setting (New onset diabetes post-transplant – NODAT). This may be due to a number of factors including weight gain and medication (especially tacrolimus and corticosteroids). As discussed below, the choice of immunosuppression must be influenced, at least in part, by the onset of diabetes. Treatment of the diabetes post-transplant is similar to that in other situations and clinicians should aim for an HBA1c target goal of <7.0% (53 mmol/mol) with a combination of lifestyle modifications and pharmacological agents as appropriate with insulins or oral hypoglycaemic agents.[8] Metformin or sulfonylureas may be used in those with normal renal function, whereas sulfonylureas such as glipizide and glimepiride are preferable in the presence of renal impairment. The newer agents such as GLP 1RA (glucagon-like peptide-1 receptor agonists) glucagon-like peptide-1 receptor agonist (such as liraglutide) and inhibitors of dipeptidyl peptidase 4 (DPP-4I) or gliptins and SGLT2i (sodium–glucose cotransporter 2 inhibitors) therapy (such as canagliflozin, dapagliflozin and empagliflozin) are likely to have a beneficial effect but formal data are missing[9] (Table 3).

Hypertension: As in the non-transplant patient, the treatment of hypertension should aim for a target goal of 130/80 mm Hg with a combination of lifestyle modifications and pharmacological agents as appropriate. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and direct renin inhibitors should be used as first-line antihypertensive therapy in liver transplant recipients with diabetes, renal impairment and/or significant proteinuria.[6,7] B-blockers may be a useful addition, but diuretics are probably best avoided.

Hyperlipidaemia: There are many causes of hyperlipidaemia, including immunosuppressive drugs (especially steroids, cyclosporine and the mTORi sirolimus and everolimus). The aim of treatment should be an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) are recommended, whereas in

Table 3 Suggested Treatment Regimens for Diabetes Mellitus in the Liver Allograft Recipient (From Bechetti et al [8]).

Co-morbidity	First line	Second line
Atherosclerotic disease	GLP 1RA	SGLT2i
Heart failure	SGLT2i	GLP 1RA
Renal impairment	SGLT2i	GLP 1RA
Obesity	SGLT2i/GLP 1RA	DPP-4i
NAFLD	Pioglitazone	DPP-4i
B-cell dysfunction	Pioglitazone DPP-4i	GLP 1RA, SGLT2i

GLP 1RA: glucagon-like peptide-1 receptor agonists.
DPP-4i: inhibitors of dipeptidyl peptidase 4.
SGLT2i: sodium–glucose cotransporter 2 inhibitors.
NAFLD: non-alcoholic fatty liver disease.

patients at high risk, an LDL-C goal of <1.8 mmol/L (<70 mg/dL) is sufficient.[9] For treatment, statins are the first line of therapy, and pravastatin is the first-line drug of choice since there is less interaction with the calcineurin inhibitors. Fibrates are well tolerated, and ezetimibe is recommended for those where statins are ineffective or not tolerated. Omega-3 fatty acids may be indicated in those with isolated hypertriglyceridemia.

Several studies have confirmed that statin use in liver transplant recipients is underused even though their use is associated with a survival benefit. Thus, a study from Virginia[10] reported that fewer than half of patients with known coronary artery disease were on therapy. Statin use conferred survival benefit (hazard ratio 0.25) and was well tolerated with only 12% of patients developing an adverse event requiring the cessation of therapy.

As cardiovascular and cerebrovascular disease is increased in liver transplant recipients, even in the absence of known risk factors,[11] there may be a case for considering statin therapy in all adult liver transplant recipients, even though there are no data to support this.

However, statins are not without significant side effects or drug interactions. There is a greater potential for interaction with cyclosporin than tacrolimus, so lower doses of statins are recommended for those on cyclosporine than tacrolimus.[12] Thus, for those on cyclosporin, lower doses of rosuvastatin, pravastatin and Fluvastatin are recommended. Side effects such as drug-induced liver injury, increased risk of diabetes, rhabdomyolysis and myopathy are possible, and clinicians need to be aware.

Obesity: Obesity is common after liver transplant and is seen especially in those who were overweight prior to transplant.[13] The reasons for weight gain are complex, and treatment is often a challenge. Clearly, changes to lifestyle, with weight reduction programmes and increased exercise will play a major role. The role of bariatric surgery is uncertain at this time[14]; there is little doubt that in carefully selected patients, in carefully selected centres, bariatric surgery is both safe and effective in helping reducing obesity and the consequent toll on health and well-being.

Renal impairment: There are many causes for renal impairment in liver allograft recipients (Table 4) and since the landmark paper by Ojo,[15] clinicians are aware of the probability of recipients developing renal impairment, leading to renal failure and the need for renal replacement therapy. Renal failure is associated with an increased risk of death (up to 4-fold) and the need for renal transplant.

Measurement of renal function post-transplant is an important part of management; serum urea or creatinine are not very sensitive, so most guidelines recommend the use of estimations of renal function, such as the MDRD formula. Measurement of proteinuria is also important as this too is a marker of renal damage. It is beyond the scope of this review to discuss in detail how renal failure should be prevented but strategies in the longer-term survivors include:

Renal impairment in the first ten post-operative days has a major impact on longer-term renal function.[16] This risk can be mitigated by a number of measures: Delayed introduction of calcineurin inhibitors has been associated with a lower risk of renal impairment. The risk of renal impairment can be reduced a number of measures including avoidance of nephrotoxic agents such as non-steroidal anti-inflammatory agents and treatment of risk factors, in particular, tight control of blood pressure and diabetes.

Calcineurin inhibitors (CNIs) are another recognised cause of renal impairment.[17] There is some evidence that late renal failure is more likely in those with higher trough levels in the first 3 months after transplant, so avoidance of high levels or delayed introduction of CNI may be advisable.[17] Immunosuppression is discussed in more detail below, but as renal impairment develops, switching to an immunosuppression regimen not based on CNI is advisable. At what point the switch should be made is uncertain. Guidelines[7] suggest switching should be considered when the estimated glomerular filtration rate is between 50 and 60 mL/min/1.73 m^2 although in my experience, this may be too late. Alternative regimens include switching to mycophenolate or azathioprine and

Table 4 Factors Contributing to Post Transplant Renal Impairment.

pre-existing renal disease,
peri-operative renal damage,
diabetes mellitus
hepatitis C or B infection,
hypertension
drug toxicity,
Calcineurin inhibitors.

corticosteroids or sirolimus or everolimus (if there is no significant proteinuria).

IMMUNOSUPPRESSION

The most common immunosuppressive regimen is based on tacrolimus, as monotherapy, as dual therapy (in combination with an antimetabolite such as mycophenolate or azathioprine or with a corticosteroid). Different units will have their own protocol, and it is beyond the scope of this review to compare the different regimens, but there are a few generalisations that can be made, based on recommendations from national and international bodies[18–20] (Table 5). Guidance for those infected with COVID-19 is also available.[21]

Review of liver histology will also allow adjustment of the burden of immunosuppression, but use of protocol biopsies to assess graft function is rarely done, because of logistic issues and the possibility of adverse consequences of biopsy.[22]

The benefits of single daily dose of tacrolimus have been suggested by large-scale registry studies[23] where there have been documented improvements in outcome as well as adherence and variability but prospective studies are required to confirm these observations.

Although those who may be operationally tolerant are being identified, strategies to test for and achieve tolerance should be done within the context of expert units only.[24]

Table 5 Some Principles Underlying Immunosuppression in Liver Allograft Recipients.

Immunosuppressive drugs have significant side-effects and the benefits need to be balanced against the risks - with infection you may lose the patient but with rejection you may lose the graft
Immunosuppression will increase the patient's susceptibility to some infections and some cancers and reduce the response to immunisation
Tailoring immunosuppression to the individual is an oft stated goal but rarely practiced
Therapeutic drug monitoring is necessary for tacrolimus, cyclosporin, sirolimus and everolimus (mTOR inhibitors) and is variably used for mycophenolate.
Target levels of immunosuppressive agents will depend on many factors including indication, time after transplant, other immunosuppressive agents, history of rejection, graft function
Typical target levels for tacrolimus are 5–8 ng/mL, for cyclosporin 75–120 ng/mL, sirolimus 4–6 ng/mL (all trough whole blood levels)
TMPT measurements for those on azathioprine is rarely indicated
Trough whole blood levels are a useful guide to immunosuppression: sub-therapeutic levels may be consistent with adequate immunosuppression and high levels may be indicative of the fact that the measured level is not a true trough level.
For many of the immunosuppressive drugs, there are several formulations. These are only sometimes interchangeable so pharmacist advice should be taken before switching patients from one brand to another
Some data suggest that single once-daily preparations of tacrolimus are associated with better outcomes that twice daily preparations
Most units aim to discontinue corticosteroids in the first year although long-term steroids are usually indicated in those transplanted for autoimmune hepatitis and other autoimmune liver diseases and those with a history of recurrent rejection.
Clinicians must be prepared to switch regimen in response to the patient's condition: this is rarely done
mTORi may be useful in those with some malignancies and a useful alternative to CNI when there is renal failure

TMPT: Thiopurine S-methyltransferase; mTOR: mammalian Target of rapamycin; mTORi: mammalian Target of rapamycin inhibitor; CNI: Calcineurin inhibitor.

ADHERENCE

Strict compliance with taking medication is a rarity in all aspects of clinical care. In the case, of liver transplantation, failure to take medication may be associated with graft rejection and occasionally graft failure. The occasional lapse is very common, and the term partial non-compliance or non-adherence is usually reserved for those occasionally miss a dose of medication. The prevalence of non-adherence is difficult to assess but estimates vary between 15 and 40%.[25] There are many risk factors that have been associated with non-compliance, but this is seen especially in paediatric and young adults. Other risk factors include concern over side effects, complexity of the drug regimen, affordability and social factors such as low family cohesion, poor social functioning, poor mental health and single-parent family.

Detection of non-adherence is difficult, and the risks do not fall with time.[6,7] The key issue is to detect non-compliance; this may be suggested by poor attendance at clinics, unexpected low trough levels of immunosuppressive agents and late acute rejection and looking for a discrepancy between the amount of drug prescribed and the need is often a useful way of confirming suspicions. The main approach is a high level of suspicion and then discussing with the patient the possibility of non-adherence, trying to work out the factors that led to non-adherence and correcting them where possible. For example, moving from a regimen that includes corticosteroids will help those with skin or other side effects and moving to a simpler regimen such as switching to once daily therapy will be effective.

Adherence is a particular issue for those in adolescence and early adulthood. Transition from paediatric to adult care is a difficult time for recipients, their families and carers as well as the medical attendants. The increasing use of transition clinics with multi-disciplinary support may help in supporting the recipient through difficult times.[26]

BONE HEALTH

Many recipients have some degree of bone loss pre-transplant, and this is exacerbated by the peri-operative

period; however, bone density may improve after the first six months.[27] Measurement of bone density should be done after the first year (if not done sooner), and if there is evidence of osteopenia, then the recipient for dietary calcium intake, serum thyroid function, gonadal function 25-hydroxyvitamin D levels, an evaluation of gonadal and thyroid function and, if abnormal, treated appropriately. The treatment of osteopenia is as for the non-transplanted patient with advice to take calcium and vitamin D supplements, stop smoking and undergo regular weight-bearing exercise, The medication should be reviewed and, where possible, corticosteroids reduced or stopped. Bisphosphonate therapy should be considered in those with osteoporosis or recent fractures. For those with progressive bone loss despite these measures, should be referred for specialist treatment.

IMMUNISATION

Live and attenuated vaccines are usually avoided in the immunosuppressed but inactivated vaccines and more recent vaccines, such as mRNA vaccines are well tolerated. The impact of immunisation may be less in the immunosuppressed than in the normal subject. Current experience with COVID vaccination[28] provides clear evidence for the benefits of vaccination.

PREVENTION OF NON-MALIGNANT RECURRENT DISEASE

Autoimmune disease: Many of the autoimmune liver diseases recur in the graft. At present, there is no effective treatment for prevention of recurrent Primary Sclerosing Cholangitis (PSC).[29] The clear evidence that colectomy either before or at transplantation protects the graft from recurrence should not be taken as an assumption that a healthy colon should be removed to present recurrence. Recurrent PSC is diagnosed by the demonstration of multiple non-anastomotic strictures in the absence of other factors (such as hepatic artery thrombosis); the diagnosis is usually made on imaging such as MRCP. For primary biliary cholangitis (PBC), treatment with ursodeoxycholic acid 13–15 mg/kg/day is associated with a lower risk of recurrent disease and longer graft survival.[30] The role of obeticholic acid and fibrates has not been fully evaluated in this context. Recurrent PBC is diagnosed by histology; anti-mitochondrial antibodies persist irrespective of recurrence; liver tests are not specific. Treatment of those transplanted for autoimmune hepatitis (AIH), should be offered long-term low dose corticosteroids as this is associated with a reduction in the risk of recurrence. Diagnosis of recurrent AIH is not always easy but is based on the presence of autoantibodies and elevated immunoglobulins and the presence of interface hepatitis on graft histology, although differentiation from rejection, especially antibody-mediated rejection, may be difficult.

Hepatitis B (HBV): A recent meta-analysis[31] concluded that prophylaxis with HBIG in combination with nucleos(t)ide analogues (NUC) gives the best results in terms of protection from recurrent disease. Studies exploring in detail high genetic barrier-to-recurrence NUC and protocols with definite use of HBIG are needed. A recent analysis by Lenci and colleagues[32] concluded that, despite initial success, concerns remain in that a standard HBV prophylaxis protocol after transplant has not yet been agreed and the emergence of strains resistant to current antiviral agents is of concern. Thus, those recipients need ongoing surveillance by an experienced team.

Hepatitis C Virus (HBV): In contrast to HBV, treatment for HCV has been revolutionised by the introduction of highly effective anti-viral treatment, so treatment is usually instigated either before or soon after transplant. Guidelines are published for the management of HCV-infected patients both before and after transplant.[33] The increasing use of organs from HCV infected donors for non-infected recipients is now well established and guidelines are being evaluated for such recipients.

Hepatocellular carcinoma (HCC): The optimal management of patients transplanted with is far from clear. Many centres do not routinely screen recipients for evidence of recurrent disease but the risks and benefits of such an approach have yet to be fully evaluated. The hope that mTORi-based immunosuppression may reduce the recurrence of HCC has not been realised.[34] However, the use of newer treatments and appropriate use of surgical and loco-regional interventions is likely to improve the outcome of those with recurrence. The use of checkpoint inhibitors is usually not indicated because of the risk of allograft rejection.

Alcohol: The return to alcohol use after transplant should be assessed as identification and intervention may improve the outcome. There are several scales and prognostic models that may help identify those at risk of a return to alcohol[35,36]; while these may identify those at risk of relapse, they should be seen as guidance rather than definitive. Ideally, those transplanted for alcohol-related liver disease should be assessed both by the medical team and specialists in alcohol and other addictions.[37] The return to alcohol consumption, whether a slip or heavy use, may be detected by asking the patient or their relatives; measurements of alcohol in breath, urine or blood will give evidence for recent use. A recent meta-analysis[38] suggested that urinary and scalp hair ethyl glucuronide are the best validated biomarkers; phosphatidylethanol is a highly promising alcohol use biomarker, but so far less validated in liver patients. Carbohydrate-deficient transferrin is not as specific as to be clinically useful. Alcohol use biomarkers

can complement each other regarding the diagnostic time window. All those grafted for alcohol-related liver disease should be questioned about alcohol use and supported by a team experienced in support.

For those transplanted for alcohol-related liver disease, who are found to have returned to alcohol consumptions should be helped to return to abstinence. For those transplanted for other indications, there is no clear consensus on how best to advise patients: few centres advocate complete abstinence, and most centres advise that alcohol should be restricted to less than 14 units/week.

Non-alcohol fatty liver disease (NAFLD): There is no specific therapy for the prevention of recurrent NAFLD, but attention should focus on risk factors such as avoidance of excessive weight gain and strict management of diabetes. Bariatric surgery is beneficial in selected patients.[39]

DE NOVO CANCERS

Allograft recipients are at risk of developing new as well as recurrent malignancies. The classification of malignancies in the liver allograft recipient is shown in Table 6.

Immunosuppression is associated with an increased risk of *de novo* malignancies.[40] As the transplant population is ageing, the risk of cancers will also increase as age itself is a risk factor for cancer. A meta-analysis[40] reported that oropharyngeal/larynx, lung, gastrointestinal, kidney, and bladder malignancies were more prevalent after liver transplant with higher standardised incidence ratio (SIR). Breast and prostate cancers were more prevalent with lower SIR. Pancreatic, CNS, melanoma, rare cancers and Kaposi's sarcoma were less prevalent with higher SIR. The age of the recipients, length of follow-up, and rare cancer types influence overall SIR values The UK experience[41] shows the 10-year incidence of *de novo* cancer in transplant recipients is twice that of the general population, with the incidence of nonmelanoma skin cancer being 13 times greater. Nonmelanoma skin cancer, cancer of the lip, posttransplant lymphoproliferative disease and anal cancer have the largest standardised incidence ratios, but the incidence of different types of malignancy differs according to the organ transplanted.

Some indications for liver transplant are associated with specific risks include an increased risk of colon cancer in those with active colitis (especially in association with PSC) and of lung and upper gastrointestinal tract cancers in those with alcohol-related liver disease.

The role of surveillance is not clear although some international guidelines have been established, but the evidence base for the cost-benefit of different regimens is not clear.[42,43] Some centres have a regular surveillance clinic for skin cancer. Most centres advocate annual colonoscopy for those with colitis and some annual chest imaging for those with a history of alcohol-related liver disease (see Table 7). The cost-effectiveness of these strategies has not been established. Certainly, it makes sense to advise recipients to avoid excess exposure to ultraviolet rays and be 'sun-sensitive' and be aware of skin lesions and seek urgent advice when new lesions develop. Smoking should be avoided, and support offered to those who continue to smoke.

Table 6 Classification of Malignancies in Transplant Recipients.

Donor transmitted cancer	Cancer is transmitted with donor organ
Donor derived malignancy	The cancer arises in the transplanted organ after implantation
Recurrent cancer	The cancer was present in the donor pre-transplant and recurs
De novo cancer	The cancer, of recipient origin, arises after transplantation

REPRODUCTIVE HEALTH

In women, menstruation and fertility usually return within the first year whereas for males, recovery of gonadal function is often incomplete. Overall, transplantation has limited efficacy for curing pretransplant sexual dysfunction. Sildenafil is beneficial and well tolerated for men with erectile dysfunction.

The return to fertility is variable. Ideally, the woman who is considering pregnancy should be fully informed about the implications of pregnancy before becoming pregnant. These are listed in Table 8. The most appropriate form of contraception will depend on the individual. The oral contraceptive and the intra-uterine contraceptive device both carry potential risks such as cholestasis and

Table 7 Possible Approaches to Enhanced Screening for *de novo* Malignancy.

Annual chest X-ray[a]
Annual chest CT[a]
Annual abdominal ultrasound
Chest and abdominal CT[a]
Annual urologic screening with PSA determination
Mammography annually
Annual Pap smear every 3–5 years
Annual skin examination by dermatologist
Upper gastro-intestinal endoscopy: annually for those with ARLD
Colonoscopy: ulcerative colitis annually
Pre-transplant adenoma 1 year, repeated every 2–4 yr if more adenomas are found.
Colonoscopy repetition every 10 yr in patients >50-yr-old
Ears, nose and throat clinic visit in patients with >20 pack year smoking

[a]Especially for smokers and ex-smokers.
CT, computerised tomography; ARLD, alcohol related liver disease; PSA, prostate specific antigen.

Table 8 Issues to be Considered Before Consideration of Pregnancy.

Fully informed about the risks and implications of pregnancy at least 1 year after transplant
there is good graft function
diabetes and hypertension (if present) are well controlled
the mother is not taking teratogenic medication such as mycophenolate or sirolimus.

thrombosis, or increased risk of infection respectively, but these risks are usually small and rarely have a significant consequences. As always, risks and benefits need to be balanced. Pregnancy in the liver transplant recipient carries some risk to both the mother and the foetus. A recent registry analysis[44] concluded that the live birth rate was 86% and the rate of other pregnancy outcomes were miscarriages (7.8%) and stillbirths (3.3%). Pooled rates of obstetric complications were hypertension (18.2%), pre-eclampsia (12.8%) and gestational diabetes (7.0%). Pooled rates of delivery outcomes for caesarean section and pre-term birth were 42% and 28%, respectively.

Post delivery, breast feeding is usually advised against as immunosuppressive drugs may be excreted in the breast milk, but some centres do suggest the benefits of breast feeding may outweigh the risks.

Table 9 Some Causes of Late (>1 year Post Transplant) Abnormalities of Liver Tests.

Some causes of late (>1 year) abnormalities of liver tests
Primary graft damage
Immune mediated rejection (T cell mediated, antibody mediated)
Infections (especially viral hepatitis A, B C or E), CMV
Recurrent disease
Drug induced liver injury
Malignancy
Abscess
Graft fibrosis and cirrhosis
Veno-occlusive disease
Graft damage secondary to vascular causes
Hepatic artery thrombosis/stenosis
Hepatic venous thrombosis/stenosis
Secondary to venous outflow obstruction
Graft damage secondary to biliary causes
Biliary strictures
Bacterial cholangitis
Ischaemic cholangiopathy (especially with grafts from donors after circulatory death)
Systemic diseases

CMV, Cytomegalovirus.

INFECTIONS

Liver allograft recipients are at greater risk of developing infections than the non-immunosuppressed and may have a more severe illness. Infectious risks agents may be viral, bacterial, fungal, protozoal or parasitic infection.[45,46] Infections may behave differently in the immunosuppressed: thus, Hepatitis E infection in the non-immunosuppressed is usually a mild and self-limiting infection but in the immunosuppressed may, if untreated, lead to chronic hepatitis and cirrhosis. Clinicians need to be aware of any recipient who becomes unwell and investigate and treat promptly. Care must be taken when prescribing antimicrobials because of drug–drug interactions. Immunosuppression needs to be reviewed and revised in those who are sick.

ABNORMAL LIVER TESTS POST-TRANSPLANT

There are many potential causes for abnormal liver tests in the liver transplant recipients (Table 9). The development of abnormal liver tests does require further investigation: usually serology (including microbiological screening) and imaging is required as a first step. Liver histology is often necessary where parenchymal disease is suspected. It is beyond the scope of this review to discuss the investigation of those with abnormal liver tests: suffice to say, abnormal liver tests should be investigated and treated as appropriate by those expert in the field and usually requires a multi-disciplinary team.

The success of liver transplantation has resulted in a dramatic increase in the number of surviving recipients, and this has posed a challenge to follow-up. There needs to be a collaboration between the patient and their medical attendants in primary, secondary and tertiary care. Outcomes of those who survive the first post-operative year has not significantly improved. Premature death is often the result of cardiovascular disease, renal failure, recurrent disease or infection. Outcomes can be improved only if the health care professionals adopt a structured approach to monitor the patient and their graft and intervene to treat those variables (including immunosuppression) that affect outcome.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

I am solely responsible for the conceptualisation and writing of the manuscript.

CONFLICTS OF INTEREST

I have no conflict of interest to declare.

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