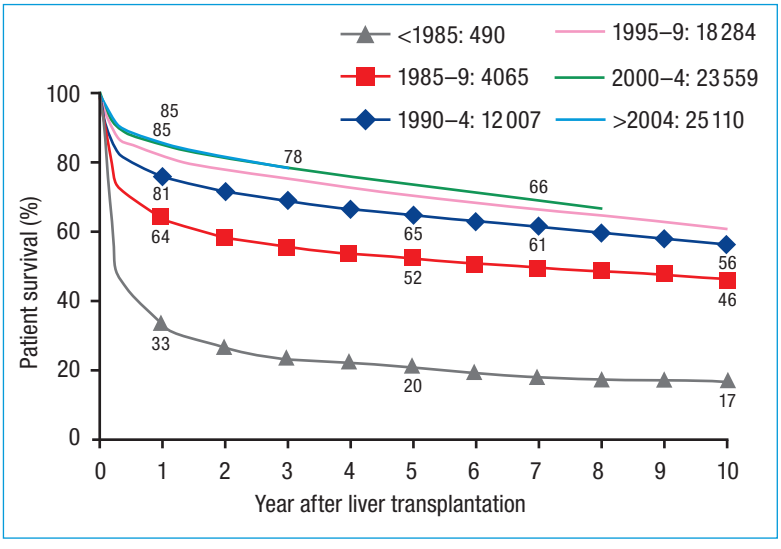
Liver transplantation: post-transplant management

ABSTRACT

Medical care for patients following liver transplantation is complex and requires a holistic approach to management. Patients and clinicians are faced with multiple challenges: immunosuppressive regimens must be optimized to avoid and treat graft rejection, the risk and atypical features of sepsis in the immunocompromised patient must be recognized, steps are required to reduce the recurrence of liver disease and the long-term increased risks of malignancy, renal failure and metabolic complications need managing. Despite the benefits of liver transplantation there are additional concerns regarding the impact upon quality of life. This review will focus upon the care of patients following liver transplantation. As these patients will present to a broad range of clinicians, an understanding of the common drugs used post-transplantation and general approach to management of these patients will be of benefit to the general clinical audience.

Figure 1. Improving survival in liver transplantation over the last 20 years. From Adam et al (2012).



In the pre-liver transplantation era patients with decompensated chronic liver disease would die within months whereas liver transplantation recipients now have survival rates in excess of 90% and 80% at 1 and 5 years respectively (Neuberger, 2016). The early survival following liver transplantation has steadily improved over the last two decades and this is likely to reflect experience in selection of patients, improved surgical technique and developments in the efficacy and tolerability of immunosuppressive therapy (Watt et al, 2010; Adam et al, 2012) (*Figure 1*).

Although liver transplantation outcomes are improving and the procedure is undoubtedly life saving for selected patients, survival after liver transplantation is significantly inferior to age-matched non-transplant recipients (Barber et al, 2007). Moreover longer term survival after liver transplantation is less impressive, with little significant reduction in late morbidity and mortality over the last two decades (Lodhi et al, 2011; Adam et al, 2012). Ten-year survival rates are 60% with the leading causes of death being cardiovascular, malignancy, infection and renal failure; liver-related mortality from chronic rejection or disease recurrence contributes to a relatively small proportion of late mortality (Watt et al, 2010) (*Figure 2*). The increasing number of liver transplants performed annually in the UK combined with improved survival following liver transplantation will result in general physicians, surgeons and GPs encountering a greater number of liver transplantation recipients in their daily practice. Thus a general awareness of the management of such patients and the longer term health problems they are likely to encounter needs to be appreciated.

Immunosuppression

Immunosuppression is routinely given after liver transplantation to block or interfere with the immune response and stop the recipient's immune system identifying the liver transplantation graft as foreign and attempting to destroy it. The common agents, their associated side effects and interactions with commonly prescribed medications are detailed in *Table 1*.

The initial choice of immunosuppression will be made by the liver transplantation centre taking into account the patient's clinical condition, aetiology of liver disease, and presence or absence of additional comorbidities (e.g. renal failure, obesity). Most centres will use a calcineurin inhibitor (tacrolimus or ciclosporin) as their principal immunosuppression with over 95% of liver transplantation recipients discharged from hospital on a calcineurin inhibitor (Wiesner and Fung, 2011). Among the calcineurin inhibitors tacrolimus is the drug of choice with superiority over ciclosporin in mortality, graft loss and episodes of rejection (O'Grady et al, 2007). In the immediate post-liver transplantation period corticosteroids are routinely used but rapidly tapered over 4–6 weeks.

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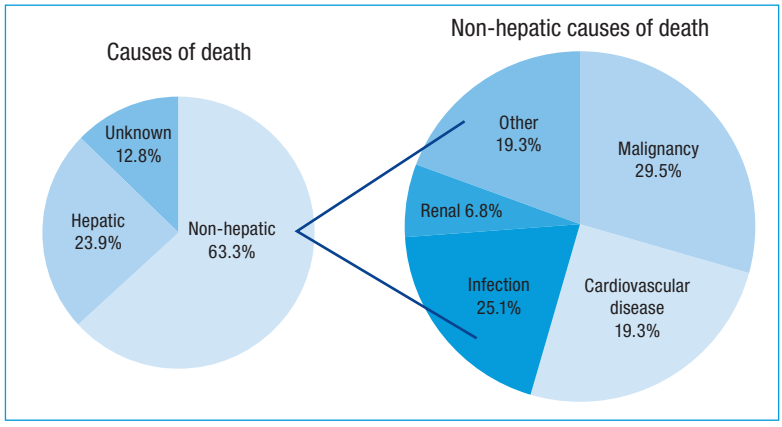
Figure 2. Causes of late mortality following liver transplantation. From Watt et al (2010).



Antimetabolites (azathioprine or mycophenolate mofetil) are often used in conjunction with calcineurin inhibitors either to augment immunosuppression to treat or prevent rejection or to reduce the dose of calcineurin inhibitor therapy when side effects (e.g. renal dysfunction) are present (Wiesner et al, 2001). Mammalian target of rapamycin inhibitors (mTOR) such as sirolimus and everolimus are currently reserved for patients intolerant to the above therapies.

In patients with renal impairment pre-liver transplantation or who develop acute kidney injury peri-transplantation, alternative induction agents can be used to avoid the immediate introduction of calcineurin inhibitor therapy and its associated nephrotoxic effects. Basiliximab is an anti-interleukin 2 receptor antibody and its use with the delayed introduction of low dose calcineurin inhibitor therapy significantly improves renal function after liver transplantation with no significant increased risk of graft rejection (Neuberger et al, 2009).

Immunosuppression therapy has revolutionized survival after liver transplantation by significantly reducing the rate of graft loss from acute and chronic rejection. However, immunosuppressive therapy itself contributes significantly to the increased morbidity and mortality which liver transplantation recipients encounter when compared to the general population, increasing the risk of malignancy, metabolic syndrome and renal failure (Leithead et al, 2012; Fussner et al, 2015; Doycheva et al, 2016) (*Table 1*). Moreover it is now becoming apparent that selected patients can achieve tolerance of the graft and immunosuppressive therapy can be withdrawn with no long-term risk to the graft, coupled with a reduction in immunosuppression-related morbidity and mortality (Adams et al, 2015). This approach is only considered in

Table 1. Common adverse effects of immunosuppressive agents used in liver transplantation

Medication	Side effects	Drug interactions	
Corticosteroids	Diabetes Hypertension Hyperlipidaemia Cosmetic changes (weight gain) Impaired wound healing Cataracts Reduction in bone mineral density Adrenal suppression		
Calcineurin inhibitors (ciclosporin, tacrolimus)	Renal impairment Hypertension Hypercholesterolaemia Diabetes (tacrolimus) Neurotoxicity – tremor, headache, confusion seizures Hirsuitism Gingival hyperplasia	Decrease calcineurin inhibitor levels	■ Anticonvulsants (carbamazepine or phenytoin) ■ Antibiotics (rifampicin, isoniazid) ■ St John's wort
		Increase calcineurin inhibitor levels	■ Antifungals (fluconazole, voriconazole) ■ Antibiotics (clarithromycin, erythromycin) ■ Calcium channel blockers (diltiazem, verapamil)
Mycophenolate mofetil	Bone marrow suppression Gastrointestinal upset (abdominal pain, nausea, vomiting, diarrhoea)		
Azathioprine	Bone marrow suppression Gastrointestinal side effects (nausea, pancreatitis) Dermatitis	Allopurinol	
Mammalian target of rapamycin (mTOR) inhibitors (sirolimus, everolimus)	Hypertriglyceridaemia Pneumonitis (sirolimus) Nephrotic syndrome (sirolimus) Mouth ulcers (sirolimus) Impaired wound healing		

highly selected patients in the setting of clinical trials, but identification of such patients is currently being evaluated via a coordinated national study within the UK.

Complications after liver transplantation

Complications following liver transplantation are best thought of in respect to their timing after the transplant operation. This is because the nature of complications and their prevalence changes as time from the liver transplantation operation evolves. Early complications, defined as a complication at <6 months from the transplant and late complications (>6 months from the liver transplantation) are outlined in *Table 2* and medical complications are expanded on below (*Table 3*).

Infections

Infectious complications are a major cause of morbidity and mortality after liver transplantation, with over 60% of recipients being affected. The prevention, early evaluation and diagnosis of post-liver transplantation infections is critical in the management of a patient post-liver transplantation. The prevalence of different infections following liver transplantation changes as the time from transplantation increases (Karuthu and Blumberg, 2012).

In the first weeks following liver transplantation the infections encountered by patients are similar to those seen in any post-surgical patient on the intensive care unit and include wound infections, pneumonia, line infections and urinary tract infection. The routine use of antimicrobial prophylaxis in the immediate post-liver transplantation period had decreased the incidence, severity and mortality from such infections (Gavalda et al, 2012).

As immunosuppressive therapy is established the patient becomes at risk of atypical infections including candida, *Pneumocystis jirovecii*, cytomegalovirus, herpes simplex virus and varicella zoster virus (Hernandez Mdel et al, 2015). A low threshold of suspicion and investigation for such atypical infections is required in any post-liver transplantation patient where infection is suspected. Cytomegalovirus and candida infection are the commonest opportunistic infections in liver transplantation recipients and have a significant morbidity and mortality if they are not treated early. In light of this many centres give routine cytomegalovirus and candida prophylaxis for the

Table 2. Complications following liver transplantation

Early <6 months	Graft	■ Primary non-function ■ Delayed graft function
	Surgical	■ Bleeding ■ Hepatic artery thrombosis ■ Venous thrombosis ■ Bile leak ■ Anastomotic stricture – biliary
	Medical	■ Infections ■ Rejection
Late >6 months	Graft	■ Ischaemic cholangiopathy
	Surgical	■ Biliary anastomotic stricture ■ Vascular stricture ■ Hepatic artery thrombosis ■ Incisional hernia
	Medical	■ Infections ■ Late rejection or chronic rejection ■ Malignancy ■ Cardiovascular disease ■ Renal impairment ■ Disease recurrence

Table 3. Long-term complications of liver transplantation

Health problem	Incidence	Risk factors	Associated immunosuppression
Mood disorders	20–25%	Hepatitis C	
Hypertension	40–85%		Tacrolimus, ciclosporin, corticosteroids
Cardiovascular disease	9–25%	Male, ethnicity, family history, hypertension, diabetes mellitus, non-alcoholic steatohepatitis	
Dyslipidaemia	45–69%		Sirolimus, ciclosporin, steroids
Diabetes	30–40%	Ethnicity, obesity, family history, pre-liver transplant diabetes	Corticosteroids, tacrolimus
Renal insufficiency	14–25%	Age, diabetes, hypertension, post-liver transplant acute kidney injury	Tacrolimus, ciclosporin
Obesity	30–35%		Corticosteroids
Malignancy	10–22%	Sun exposure, smoking	Ciclosporin, tacrolimus, azathioprine
Bone disease	30–35%	Poor nutrition, immobility, smoking, sarcopenia, smoking, alcohol	Corticosteroids, ciclosporin

first 3 months post-liver transplantation to cover the time when immunosuppression levels are often at their highest (Eschenauer et al, 2009; Mumtaz et al, 2015).

Fever in the post-liver transplantation patient is an emergency – it must always be investigated and antibiotics started early if bacterial infection is suspected. Prevention strategies are important and all liver transplantation patients should be immunized against influenza and pneumococcus; hepatitis B and A vaccination should have been administered pre-liver transplantation. It is recommended that live vaccines are avoided following liver transplantation.

Graft rejection

Acute and chronic graft rejection are beyond the scope of this article. However, it should be noted that acute cellular rejection is common and mild acute cellular rejection is managed by augmentation of baseline immunosuppression. In moderate or severe rejection intravenous corticosteroids are typically used.

Metabolic syndrome and cardiovascular disease

Cardiovascular disease is increased significantly above that of the general population following liver transplantation. Death from cardiovascular disease is the leading cause of non-liver-related late mortality, accounting for almost 25% of deaths after 5 years (Watt et al, 2009; Desai et al, 2010; Madhwal et al, 2012). The reasons for this significant mortality are multifactorial. The metabolic syndrome, which incorporates insulin-resistant diabetes mellitus, obesity, dyslipidaemia and arterial hypertension, affects between 50 and 60% of post-liver transplantation recipients (Watt and Charlton, 2010). Individually reported studies describe the prevalence of diabetes mellitus in 10–64% of liver transplantation recipients, obesity (body mass index >30 kg/m^2) in 24–64%, dyslipidaemia in 40–66% and arterial hypertension in 40–85% (Lucey et al, 2013; Luca et al, 2015).

Immunosuppression therapy is recognized to either exacerbate or cause de novo arterial hypertension, diabetes, dyslipidaemia and obesity in the post-liver transplantation population (Barnard et al, 2016), thus increasing cardiovascular risk (*Table 3*). Moreover the conventional risk factors that place a patient at risk for the metabolic syndrome are often prevalent in pre-liver transplantation populations such as those transplanted for non-alcoholic fatty liver disease. Smoking is common in certain disease aetiologies pre-liver transplantation, including hepatitis C and alcohol-related liver disease, and continuing to smoke further compounds the risk of cardiovascular disease post-liver transplantation.

Aggressive management of cardiovascular disease risk factors post-liver transplantation and immunosuppressive minimization where possible is essential if a positive impact on late morbidity and mortality is to be achieved. Hypertension should be aggressively treated with a target blood pressure of 130/80 mmHg. First-line antihypertensive therapies are dihydropyridine calcium-channel blockers (amlodipine or nifedipine). Statin therapy should be considered and commenced in patients with cardiovascular disease, type 2 diabetes and those with an elevated 10-year cardiovascular disease risk of greater than 7.5%. Statin therapy may interact with calcineurin inhibitors, resulting in increased statin concentrations and risk of rhabdomyolysis as both are metabolized by cytochrome P450-3A4. Pravastatin and fluvastatin are the statins of choice post-liver transplantation as they are not metabolized by the cytochrome P450-3A4. Finally the benefit of education regarding a healthy diet and regular exercise programmes should not be forgotten.

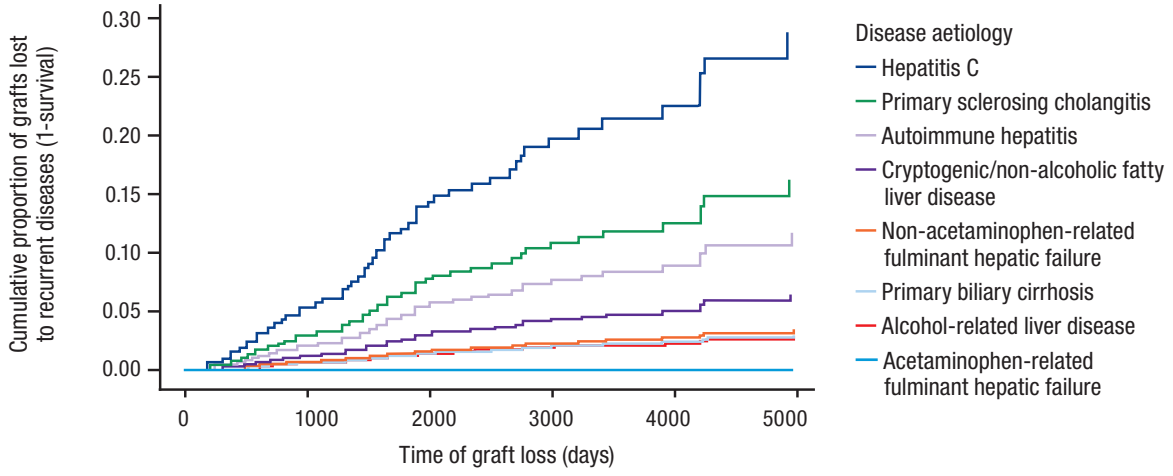
Malignancy

De novo malignancy after cardiovascular disease is the leading cause of late morbidity and mortality after liver transplantation. Liver transplant recipients have a 2–3-fold increased risk of solid organ cancers, a 30-fold increase in lymphoproliferative cancers and up to 70-fold increase in squamous or basal call skin carcinomas compared to the general population (Watt et al, 2009). The risk of solid organ cancers increases with time from liver transplantation (Engels et al, 2011). Risk reduction is focussed on controlling modifiable risk factors including immunosuppression minimization, sun avoidance, alcohol and smoking cessation, but many risk factors (immunosuppression, aetiology for liver transplantation, increasing patient and graft age) cannot be modified (Carenco et al, 2015). Despite the recognized increased relative risk of de novo cancers in the liver transplantation population, cancer surveillance strategies have yet to definitively prove an overall impact on cancer-related mortality.

Patients with alcohol-related liver cirrhosis as their indication for liver transplantation are particularly at risk of upper gastrointestinal, oropharyngeal and lung cancers. A smoking history pre- and post-liver transplantation further increases the risk of head, neck or lung carcinoma, highlighting the importance of smoking cessation pre- and long-term post-liver transplantation (Watt et al, 2009; Herrero et al, 2011). Patients with primary sclerosing cholangitis and associated inflammatory bowel disease are at a significantly increased risk of colorectal carcinoma and annual screening colonoscopies are recommended in such patients (Watt et al, 2009).

Post-transplant lymphoproliferative disorder primarily affects younger recipients and can occur any time following liver transplantation. Epstein–Barr virus has an aetiological role in 80% – it causes proliferation of B lymphocytes which, in the context of immunosuppression is not inhibited, resulting in mutations and post-transplant lymphoproliferative disorder. Symptoms include fever, weight loss, night sweats and lymphadenopathy; cytopaenias and a raised lactate dehydrogenase level on a blood count are suggestive, but histology is required for a definitive diagnosis. Management is a reduction in immunosuppression and if unsuccessful chemotherapy.

Figure 3. Graft loss secondary to disease recurrence by aetiology of liver disease. From Rowe et al (2008).



Disease recurrence

Certain liver pathologies resulting in the need for liver transplantation can reoccur following liver transplantation, with the frequency varying depending on the primary disease (*Figure 3*). Conversely other causes of chronic liver disease are cured by liver transplantation; these include alpha-1 anti-trypsin deficiency, haemochromatosis and Wilson's disease.

To date hepatitis C is reported as having the highest rate of recurrence post-liver transplantation, occurring in 100% of those patients who were hepatitis C virus RNA positive at the time of liver transplantation (Westbrook and Dusheiko, 2014). Progression of hepatitis C is accelerated following liver transplantation resulting in hepatitis C-infected recipients having poorer graft and patient survival (Forman et al, 2002). Such patients should undergo regular assessment of graft fibrosis via a combination of some or all of transient elastography, liver histology and indirect measurement of portal pressure to identify those at greatest risk and who will benefit from early hepatitis C virus treatment. However, given the recent advent of and increased access to direct-acting antiviral therapy it is now the norm for hepatitis C virus to be eradicated before liver transplantation. Interferon-free, direct-acting antiviral regimens allow eradication of hepatitis C virus infection, with high efficacy, in patients with decompensated liver disease while awaiting transplantation, meaning this will become a much rarer cause of disease recurrence post-liver transplantation in the future (Gambato et al, 2014; Charlton et al, 2015). In those patients with hepatitis C recurrence following transplantation, there is growing evidence that direct-acting antiviral drugs have high sustained virological response rates despite immunosuppression (Suraweera et al, 2016). However, some regimens require careful monitoring and dose adjustment because of interactions with calcineurin inhibitors.

Hepatitis B virus can be prevented post-liver transplantation by the use of hepatitis B immunoglobulin in the immediate post-liver transplantation period and nucleoside analogues (tenofovir/entecavir) long term (Gane et al, 2007; Fung et al, 2013).

Recurrent or de novo non-alcoholic fatty liver disease is commonly seen post-liver transplantation as a result of the increased prevalence of the metabolic syndrome secondary to use of immunosuppressants and its preventative management is detailed above.

The autoimmune liver diseases including primary biliary cirrhosis, autoimmune hepatitis and primary sclerosing cholangitis can all re-occur post-liver transplantation in 10–50% of recipients, although actual rates of graft loss are significantly lower especially in primary biliary cirrhosis (El-Masry et al, 2011).

Relapse rates to alcohol following liver transplantation for alcohol-related liver cirrhosis are highly variable (10–50%) secondary to no accepted definition of relapse (Faure et al, 2012). While occasional drinking may not impact on graft survival, 20% of relapsers will progress to harmful drinking which impacts on graft and patient survival (Faure et al, 2012).

Finally patients transplanted for hepatocellular carcinoma within Milan criteria have a risk of hepatocellular carcinoma recurrence between 8 and 20% during the first 2 years with an associated very poor prognosis (Clavien et al, 2012).

Renal disease

Renal disease is a well-recognized complication post-liver transplantation and is associated with an increase in long-term morbidity and mortality. Aetiology is multifactorial contributed to by calcineurin inhibitor therapy, renal dysfunction pre-liver transplantation, perioperative acute renal failure, diabetes and hypertension. Overall approximately 50% of post-liver transplantation patients with develop chronic kidney disease stage 3/4, with 5–9% requiring dialysis by 10 years post liver transplantation (Ojo et al, 2003).

All liver transplantation patients should avoid nephrotoxic drugs (non-steroidal anti-inflammatory

KEY POINTS

- Liver transplantation offers a survival benefit for patients with acute and chronic liver diseases and primary liver cancer.
- Immunosuppressive medications have interactions with many commonly prescribed drugs and prescribers should be aware of these.
- Immunosuppression regimens are individualized depending upon primary liver disease, rejection, comorbidities and intolerances.
- The range of common infections affecting post-transplant patients differs from the general population and changes with time from transplantation.
- Acute cellular rejection is typically an early complication following transplantation.
- Patients are at increased risk of metabolic, cardiovascular, malignant and renal complications.
- Despite the clear mortality benefit for patients there are concerns regarding quality of life outcomes for some patients.

drugs) and should have their hypertension and diabetes aggressively controlled. In patients with progressive renal disease changing immunosuppressive therapy to a calcineurin inhibitor-sparing or calcineurin inhibitor-free regimen should be considered by the transplant centre.

Quality of life after liver transplantation

As discussed above, although life-saving, liver transplantation carries significant medical and surgical morbidity and mortality and many patients have valid concerns regarding quality of life following liver transplantation as opposed to merely increased length of survival.

Quality of life has been assessed post-liver transplantation in several short-term studies which have demonstrated encouraging results, but data on the longer term evaluation of quality of life are less convincing (Yang et al, 2014). Physical and mental functioning along with life satisfaction scores improve short- and long-term post-liver transplantation (De Bona et al, 2000). However, data regarding anxiety and depression show convincing short-term improvement but less convincing longer term outcomes with anxiety regarding disease recurrence and side effects of medication predominating. The percentage of liver transplantation recipients who return to work after transplantation averages about 40%, with improved reported quality of life in those employed *vs* unemployed (Aberg et al, 2012).

Sexual dysfunction improves post-liver transplantation but remains problematic with high rates of erectile dysfunction, reduced libido and difficulty reaching orgasm. For women of childbearing age fertility is restored and with it come realistic prospects for starting a family.

Overall, quality of life studies in post-liver transplantation patients are similar to those in kidney, heart and lung transplant recipients, but are inferior to those of sex- and age-matched healthy individuals.

Conclusions

Following liver transplantation, patients have complex care needs and optimal care will reduce the risk of recurrence of the primary liver disease, protect the graft from rejection and minimize the risk of complications of immunosuppressive drugs. Despite this there is an increased risk of malignancy, renal failure, metabolic and cardiovascular diseases. Focussed assessment and optimization of these risks is key to improving long-term survival, which remains below age-matched, non-transplanted controls. **BJHM**

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