Chapter 17
Liver Transplantation

Rohit Gupta and James O'Beirne

Key Learning Points

- Liver transplantation is a life-saving treatment for selected patients with severe forms of liver disease.
- Models exist to predict the severity of liver disease and need for liver transplantation, e.g. United Kingdom end-stage liver disease score (UKELKD), the model of end-stage liver disease (MELD) these scores can also be used to prioritize patients on the waiting list and in conjunction with donor factors are useful for allocation of organs to maximize transplant benefit.
- Patients with chronic liver disease including acute on chronic liver failure, acute liver failure, hepatocellular carcinoma and variant syndromes have access to liver transplantation.
- Prior to listing a comprehensive assessment of patient fitness, addiction behaviours and psycho-social factors must be performed.
- Patients listed for liver transplant must have a minimum expected survival of 50% at 5 years from transplant.

R. Gupta · J. O'Beirne (✉)
Department of Hepatology, Sunshine Coast University Hospital, Birtinya, QLD, Australia
e-mail: James.OBeirne@health.qld.gov.au

T. Cross (ed.), *Liver Disease in Clinical Practice*, In Clinical Practice, https://doi.org/10.1007/978-3-031-10012-3_17

Case Study

A 65-year-old man with non-alcoholic steatohepatitis cirrhosis presented to the outpatient clinic. He had portal vein thrombosis and chronic hepatic encephalopathy with three admissions in the previous year despite lactulose and rifaximin. Laboratory workup was remarkable for INR 1.1, creatinine 105 μmol/L, bilirubin 22.3 μmol/L, sodium 141 and albumin 30 g/L. This patient had Child-Pugh Class B cirrhosis (7 points) and the UKELD and MELD scores were 48 and 10 points, respectively.

Questions

1. Should this patient be referred for liver transplantation based on the severity of his liver disease?
2. What aspects of the patient's medical history should be examined closely during transplant assessment?
3. Is the patients age a barrier to receiving a liver transplant?

Introduction

Thomas Starzl and colleagues performed the first successful liver transplant in humans in 1963 and since then liver transplantation (LT) has revolutionized the care of patients with acute and chronic liver failure of all aetiologies refractory to medical therapy [1]. Currently LT is a common practice worldwide with survival rates reaching 96% at 1 year for elective procedures in low risk patients [2]. As safety and early survival has improved over time, so has the number of indications and candidates who may benefit leading to the current organ shortage.

Despite improvements in early survival rates there has been a less impressive increase in long-term survival reflecting the challenge of long-term management of LT recipients, a population under lifelong immunosuppression with increased risk of renal failure, cardiovascular events and malignancies.

Candidates

Careful patient selection is essential for the short- and long-term success of liver transplantation. LT should be considered in patients with irreversible and progressive liver disease without an alternative therapy in whom it is expected that LT will prolong life. Patients with an anticipated life expectancy without LT of 1 year or less should be considered for LT. As donor organs are scarce, attention must be paid to the expected outcome following LT. Patients should expect to have at least 50% chance of survival at 5 years [3]. A number of different models based on biochemical parameters are used throughout the world to identify candidates with a poor prognosis that might benefit from LT (MELD, UKELD). These scores allow for the establishment of a minimal listing threshold below which LT is not likely to add benefit. They also allow stratification of listed patients such that patients with more severe disease are afforded priority. Increasingly factors related to the donor and graft are considered in allocating organs to recipients in order to maximize 'transplant benefit' [4].

Indications for Liver Transplantation

Potential LT candidates can be broadly divided into five groups:

1. Patients with chronic liver disease (cirrhosis), of any aetiology, who develop a complication, namely ascites, spontaneous bacterial peritonitis (SBP) hepatic encephalopathy, variceal bleeding (particularly after medical therapy failure), synthetic dysfunction (hyperbilirubinaemia and/or coagulopathy) or worsening renal function.
2. Patients with acute liver failure (ALF) of any cause, defined by the development of hepatic encephalopathy within 12 weeks of the onset of acute liver injury and/or jaundice without previously recognized chronic liver disease.

3. Liver tumours, most commonly, patients with early hepatocellular carcinoma meeting specific criteria who are not candidates for resection.
4. Variant syndromes where mortality risk is not reflected by commonly used prognostic scores such as MELD and UKELD. For example: hepatopulmonary syndrome, recurrent cholangitis, hepatic encephalopathy (requiring two or more hospital admissions within a 6-month period) and diuretic refractory ascites.
5. Metabolic or genetic diseases characterized by near-normal liver architecture and severe extrahepatic manifestations such as familial amyloid polyneuropathy, primary hyperoxaluria and familial hyperlipidaemia.

Increasingly, other indications for liver transplantation are being evaluated such as transplantation for cholangiocarcinoma, colorectal liver metastases and acute on chronic liver failure. These advances have been enabled by better understanding of the natural history of the disease and expanded access to previously unusable organs through the use of machine perfusion technology [5].

In Europe, 148,421 LT were performed between 1988 and June 2020, most of which were due to cirrhosis (54%), followed by cancers (18%) and cholestatic/congenital diseases (7%) [6]. ALF was responsible for 8% of LT performed in this period [6].

Prognostic Scoring Systems for End-Stage Liver Disease

The selection of patients and the timing of transplantation are key determinants for patient outcomes. Patients who are transplanted too early will be exposed to the risks of surgery and immunosuppression, whereas patients referred too late may be too sick for intervention. To help clinicians in this decision process, prognostic scoring systems have been developed to determine the need for transplantation (minimal listing criteria) and prioritize them in the waiting list based on liver disease severity and risk of mortality.

The Model of End-Stage Liver Disease (MELD)

MELD was developed in 2000 to determine the 3-month survival of patients with end-stage liver disease (ESLD) who underwent a TIPS placement after gastrointestinal bleeding. A modification was adapted to predict 90-day mortality of patients waiting for LT and replaced the Child-Pugh scoring system used in the USA since 2002. MELD has now been adopted in most liver transplantation networks to prioritize listed patients. The variables of MELD equation are serum bilirubin, creatinine and INR. Children under the age of 12 are assessed with a different system, the Paediatric End-Stage Liver Disease (PELD) score that does not include creatinine and uses bilirubin and INR (similarly to the MELD score) and albumin, age, growth failure.

MELD is used to prioritize patients for LT. A MELD of 15 is the point at which LT would be expected to improve 1 year survival and naturally, the higher the score the greater chance of dying and thus a higher priority for LT. Of note, this score also predicts mortality after LT in patients with MELD >35.

Modification of MELD (MELD-Na)

Since the adoption of MELD in liver transplant centre, attempts have been undertaken to further optimize the score. The most promising and frequently used score is the MELD-Na. This score incorporates serum sodium level with the MELD score and has shown to improve the prediction of mortality than the standard MELD and may also reduce listing mortality rate.

The United Kingdom Model for End-Stage Liver Disease (UKELD)

UKELD is a mathematical model that predicts mortality from liver cirrhosis. It was created from patients listed for LT at all UK liver transplant units and later validated in an inde-

pendent prospective cohort. UKELD has now been adopted in all UK centres. The score is derived from serum bilirubin, creatinine, sodium and INR. Patients fulfil minimal listing criteria for LT when the UKELD is ≥49. This cut-off is used because it predicts a 1-year mortality of ≥9% without LT compared to the 9% 1-year mortality after LT. Since there are conditions that benefit from LT, but that are not mirrored by the UKELD score, the UK NHS Blood and Transplant Health Authority defined the variant syndromes that include patients that can be listed for LT even if their UKELD is lower than 49 (Table 17.1).

Table 17.1 Potential candidates for liver transplantation

1. Chronic liver disease with MELD ≥15 or UKELD ≥49 points
Alcoholic liver disease
Non-alcoholic fatty liver disease
Chronic viral hepatitis: Hepatitis B, C and D
Autoimmune liver diseases: Autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis and overlap syndromes
Genetic diseases with predominant liver parenchymal damage: Genetic hemochromatosis, Wilson's disease, alpha-1-tripsin deficiency and tyrosinaemia
Secondary sclerosing cholangitis
Graft versus host disease
Budd-Chiari syndrome
Cryptogenic cirrhosis
2. Acute liver failure
Acetaminophen poisoning
Sero-negative or indeterminate
Amanita phalloides ingestion
Viral infections (e.g. hepatitis B)
Wilson's disease
Acute fatty liver of pregnancy
Autoimmune hepatitis
Primary non-function of liver graft

Table 17.1 (continued)

3. Malignant disease
Hepatocellular carcinoma
Epithelioid hemangio-endothelioma (can also be categorized as a variant syndrome)
Hepatoblastoma
Cholangiocarcinoma
4. Variant syndromes
Diuretic resistant ascites (unresponsive or intolerant to maximum diuretic dosage and nonresponsive to TIPS or where TIPS is not feasible)
Chronic hepatic encephalopathy (confirmed by EEG or trail making tests with at least two related admissions in 1 year not responsive to medical therapy)
Intractable pruritus (after excluding a contributing psychiatric co-morbidity)
Hepatopulmonary syndrome
Recurrent cholangitis (refractory to medical, surgical and endoscopic therapy)
Genetic diseases associated with severe or life-threatening extrahepatic complications: Crigler Najjar syndrome, urea cycle disorders, familial amyloid polyneuropathy (FAP), primary hyperoxaluria type 1, familial hypercholesterolaemia, glycogen storage disease [2] and atypical haemolytic uremic syndromes
Polycystic liver disease

Adapted from the NHS Blood and Transplant Health Authority Policy 195/4 Liver transplantation: Selection criteria and Recipient Registration, March 2015

Super-Urgent LT

The indications and rules for urgent priority LT are similar in most European centres and include patients with acute liver failure (ALF) and patients with primary graft non-function of the liver (PGNF) or graft failure due to vascular complications early after transplant. These patients represent a singular group of LT candidates compared to patients with chronic liver disease, with a shorter time frame for (re)assessment and (re)listing due to high short-term mortality without transplant.

Table 17.2 Absolute and relative contraindications to liver transplantation

Absolute	Relative
– Psychological, physical and social inability to tolerate the procedure and comply with post-transplant treatments – Active and uncontrolled sepsis – Active extrahepatic, metastatic malignancy or cholangiocarcinoma[a] – AIDS – Advanced cardiopulmonary disease – Extensive portal and mesenteric vein thrombosis – Irreversible and severe brain damage – HCC and tumour rupture, extrahepatic spread or AFP >1000 ng/mL	– Age older than 65 and younger than 2 – Portal vein thrombosis – Prior porta-caval shunt – Prior complex hepato-biliary/abdominal surgery – Obesity (BMI ≥40 kg/m^2) or malnutrition – HIV – Renal impairment (predictor of post-LT death) – Active alcohol and/or substance abuse – History of cancer <5 years

[a]Absolute contraindication in most centres. In case of perihilar cholangiocarcinoma LT can be offered in specialized centres with clinical research protocols

ALF patient selection for emergent LT is usually based on the King's College Hospital criteria (Table 17.2).

ALF secondary to paracetamol overdose:

1. pH <7.25 (>24 h post overdose) or
2. INR >6.5 (PT >100 s) and serum creatinine >300 μmol/L (>3.4 mg/dL) in patients with grade 3 or 4 hepatic encephalopathy.

Non-paracetamol associated ALF:

1. INR >6.5 (PT >100 s), or
2. Any three of the following:

Age <10 or >40 years; aetiology non-A, non-B hepatitis or idiosyncratic drug reaction; duration of jaundice before hepatic encephalopathy >7 days; INR >3.5 (PT >50 s); serum bilirubin >300 μmol/L (>17.6 mg/dL).

Malignant Liver Disease

Hepatocellular carcinoma (HCC) is the most common malignant cause for LT. It should be considered in patients with early HCC that is not resectable due to its location or concerns related to poor synthetic function and features of portal hypertension (e.g. hepatic venous pressure gradient ≥10 mmHg). Recurrent disease following LT is problematic for patients with advanced disease and hence LT is limited to patients with early HCC. The most widely used are the Milan Criteria. These help define patients with HCC and liver cirrhosis with a low risk of recurrence post-LT [7]. The Milan criteria are: one lesion with a diameter <5 cm or up to three nodules each ≤3 cm and no vascular invasion or metastatic disease. As experience has grown in the use of LT for HCC a number of groups have expanded cautiously on the Milan criteria. For instance, The University of California San Francisco (UCSF) criteria expand the number of patients eligible for LT by including single tumours up to 6.5 cm and several nodules, the largest up to 4.5 cm, as long as the total sum of all diameters is <8 cm. The recurrence free survival is similar when applying the UCSF and Milan criteria and guidelines now recommend that an expansion of the Milan Criteria is acceptable if recurrence free survival is comparable.

In the UK, listing criteria have been expanded beyond the Milan Criteria, since it was shown that some patients who had acceptable rates of recurrence were denied LT using the Milan criteria. The current UK criteria are: alpha feto-protein <1000 ng/mL, a single tumour diameter ≤5 cm, up to 5 nodules all ≤3 cm or a single tumour 5–7 cm without significant progression over 6 months with or without loco-regional

therapy. In addition, HCC patients outside these criteria, who have undergone down staging loco-regional therapy may be listed if they fulfil recently defined criteria that reflect 'good' tumour biology [8].

In recent years several institutions have undertaken liver transplantation for the indications of perihilar cholangiocarcinoma. The Mayo protocol has been incorporated in these centres for patient selection. The protocol's inclusion criteria are perihilar cholangiocarcinoma unable to be resected that is less than 3 cm in patients who have no evidence of metastasis. Patients receive neoadjuvant chemotherapy prior to transplantation. Other indications such as strictly selected patients with oligo-metastatic colorectal cancer liver metastases are emerging. Whether these newer indications become established will depend on demonstrating equivalent outcomes to accepted indications and the availability of organs.

Absolute and Relative Contraindications to LT

Absolute contraindications include advanced and uncorrectable cardiopulmonary disease, ongoing infection, active extrahepatic malignancy, irreversible severe brain injury and inability to comply with post-transplantation treatment (Table 17.2).

Relative contraindications include factors related to the candidate fitness, past medical history and liver disease itself, which may increase the risk of LT in that particular patient, and outweigh the expected benefits such as portal vein thrombosis.

Advanced age is not a barrier to LT; however, patients ≥65 years have an increased risk of cardiovascular complications and should only be listed after a thorough assessment to exclude significant medical co-morbidities.

Active alcohol intake and substance abuse is an area of controversy and guidelines vary according to centres and countries. In many centres a 6 month abstinence period is

mandated prior to LT. This period is considered beneficial since it identifies patients with a lower risk of relapse to alcohol use post-LT and, importantly, allows time for liver injury to recover such that LT may be avoided. The concept of an enforced period of abstinence can be challenged. For instance, there is limited evidence correlating the length of pre-treatment abstinence with post-transplant abstinence. Furthermore for patients with grade 3 acute on chronic liver failure (ACLF) or alcoholic hepatitis (AH) an enforced period of abstinence is unrealistic given the very high short-term mortality. Many centres worldwide now have protocols in place for transplantation of these very sick patients and report good outcomes (see below). Patients being considered for LT with a background of alcohol or substance misuse should be assessed by specialists in addiction to determine the risk of relapse following LT. Overall, the influence of relative contraindications on suitability for LT depends on the expertise of the transplantation team and should be assessed on a case-by-case basis.

An emerging and likely effective therapy for alcoholic hepatitis is liver transplantation. The seminal work by Mathurin et al. showed a significant 1 year survival benefit with liver transplantation of 77% compared to 23% with current management in the setting of life-threatening alcoholic hepatitis [9]. The average MELD in these patients was 34. The selection criteria for liver transplantation in these patients include: first liver decompensating event in patients, Maddrey discriminant function >32 and classified as a non-responder to corticosteroids with Lille score >0.45. The ACCELERATE-AH consortium in the US has published results of liver transplantation in 147 patients with life-threatening alcohol hepatitis achieving a 1 year survival of 94% and 84% at 3 years [10]. The mortality without transplant in this patient group would usually be 70% in 6 months showing the significant benefit of liver transplantation. Whilst scarcity of organs and patients selections have limited universal acceptance, the results show a clear mortality benefit.

Following assessment, the decision to list a patient for LT is ultimately made after a multidisciplinary discussion at a liver transplant centre involving transplant physicians, surgeons, anaesthetists, intensivists, dieticians and addiction and alcohol specialists. Once on the list patients undergo regular reassessment to ensure that they have developed no contraindications to LT. Patients may be withdrawn from the waiting list if there is a favourable clinical course after listing such that no need a LT criteria.

Pre-transplant Assessment

Pre-LT assessment is a fundamental step that allows the transplant team to identify and correct factors that may have a negative impact on LT outcome and/or bring to light conditions that are contraindications, e.g. extrahepatic malignancies.

Cardiopulmonary Assessment

All candidates should undergo an electrocardiogram and transthoracic echocardiogram. Patients with multiple cardiovascular risk factors should also undergo a cardiopulmonary exercise test (CPET) or a pharmacological stress test (nuclear medicine cardiac ischaemic studies, e.g. myoview, or dobutamine stress test) to rule out asymptomatic ischaemic heart disease. If coronary heart disease (CHD) is suspected a coronary angiogram should follow.

A lung function test and chest X-ray are the first line studies to assess respiratory function. If hepatopulmonary syndrome is suspected the alveolar-arterial oxygen gradient should be calculated and contrast echocardiography should be performed. Patients with evidence of pulmonary hypertension on echocardiography should undergo right heart catheterization to confirm this diagnosis. Moderate (mean pulmonary artery pressure $\geq$35 mmHg) and severe

(≥45 mmHg) PPHTN are associated with increased mortality after LT and should addressed with pulmonary vasodilators before LT.

Renal Assessment

Renal dysfunction has a negative impact on short-term survival after LT. All patients should have glomerular filtration rate estimated and urinalysis and renal ultrasound are recommended. A renal biopsy may be necessary to clarify the aetiology of renal dysfunction. A combined liver–kidney transplant should be considered in patients with GFR <30 mL/min or hepato-renal syndrome requiring renal replacement therapy for more than 8–12 weeks.

Imaging

A contrast CT scan of the chest and abdomen is mandatory to visualize the splanchnic vasculature, particularly, the hepatic artery and main portal system, in order to plan the surgical procedure. Alternatively, a MRI may be used, especially in patients with renal dysfunction and or HCC. Magnetic resonance cholangio-pancreatography is useful in the assessment of patients with sclerosing cholangitis. Occasionally, diagnostic ERCP may be required in this setting, e.g. patient unable to tolerate MRI.

Nutritional Assessment

An assessment by an experienced dietician is mandatory and malnutrition and sarcopenia should be addressed prior to LT. A bone densitometry is also part of the pre-transplant workup since osteoporosis is common in patients with liver cirrhosis. Frailty and sarcopenia have poor prognostication in the setting of cirrhosis and liver transplantation. The Liver Frailty Index (LFI) involves a simple bedside functional assess-

ment of sarcopenia involving grip strength, chair stands and balance testing. Patients with a LFI of >0.45 defined as frail are recommended to be optimized prior to transplantation.

Finally, social and psychiatric assessment and counselling are vital to address potential risk factors for non-adherence and addictive behaviours prior to LT, including smoking cessation. All patients are strongly advised to stop smoking to reduce the cardiovascular and risk of malignancy that are exacerbated as a consequence of LT.

Liver Graft Allocation

In most organizations, when a deceased donor organ becomes available priority is given to super-urgent cases. If the organ is declined or there is no suitable recipient, then it is directed to elective LT in which organ allocation can be patient-directed or centre directed. In a centre oriented system the organ is allocated to a specific centre, and the decision of which patient will receive the organ is made by the centre's multidisciplinary team based on the internal prioritization system. In a patient-directed allocation system a particular organ is 'matched' to a recipient in order to maximize 'transplant benefit'.

The majority of liver grafts originate from deceased donors and can be further divided into donation after brain death (DBD) and donation after circulatory death (DCD).

In order to address organ shortage additional sources of organs are being used: such as 'marginal donors' and living donors. The so-called marginal donors or extended criteria donors (ECD) are donors with unfavourable features and traditionally associated with poorer graft and patient survival and include individuals with advanced age, significant steatosis, hepatitis B core antibody and HCV positive donors and DCD. DCDs are included in this group because they can associated with severe ischaemia-reperfusion injury, and also primary graft non-function, delayed graft function and biliary ischaemia. Scores have been developed to quantify the risk of graft failure by using these ECD, including the donor index

risk and the 'balance of risk' score. In recent years the use of machine perfusion techniques which perfuse the retrieved organ and replenish ATP and other metabolites has been shown to be effective at preventing damage associated with cold storage whilst simultaneously allowing assessment of likely function once implanted. These techniques have increased the utilization and safety of previously unusable grafts and expanded the donor pool.

In live donor transplantation a partial liver graft is obtained usually from a family member or a close friend. The technique was initially used in children but has now been expanded for adults who usually receive the right lobe of the donor. In parts of Asia this is the commonest form of liver transplantation whereas in the USA and Europe live donor transplantation in adults is still infrequent mainly due to the very small risk to the donor.

The donor graft pool could be increased by splitting a cadaveric donor liver for two recipients usually an adult and a child. Partial grafts can also be used in auxiliary LT, in which a partial graft is introduced leaving the native liver in situ. This technique is occasionally used in ALF to support the patient's diseased liver whilst it recovers, and in patients with metabolic defects in which case the grafted liver corrects the metabolic disorder, without the need for a complete LT surgery.

Finally, domino LT is a process whereby a liver from a patient with familial amyloid polyneuropathy (FAP) (in who complications have developed but who otherwise have normal liver function) donate their liver. The recipient should be over 55 years to minimize the risk of the neurological consequences of FAP.

Liver Transplant Surgery

The donor organ is dissected and pre-cooled through the portal vein with Ringer's lactate. Secondly, the liver is perfused with 1000 mL of University of Wisconsin (UW) solution through the aorta and portal vein. The graft is then

removed, flushed with 1000 mL of UW solution through the hepatic artery and stored in this solution in a plastic bag, afterwards placed on ice in a portable cooler. This retrieval technique has allowed for the liver preservation time to be extended up to 18 h.

In the recipient, the hilar structures and vena cava above and below the liver are dissected. The native liver is then removed after cross-clamping all the vascular structures and the new liver implanted in the right upper quadrant. Most European centres now use the piggy-back technique that preserves the recipient's inferior vena cava by anastomosing it side-to-side to the donor IVC (Fig. 17.1). The traditional

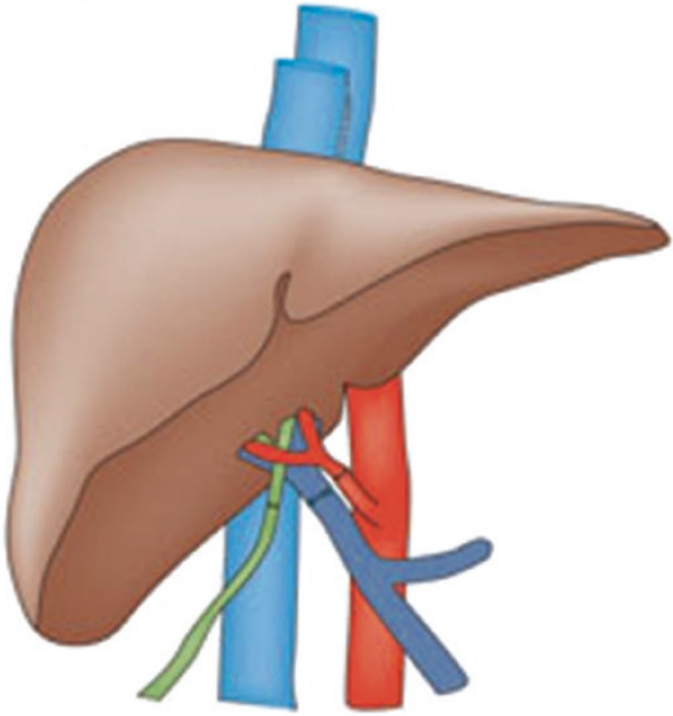

Figure 17.1 Piggyback technique

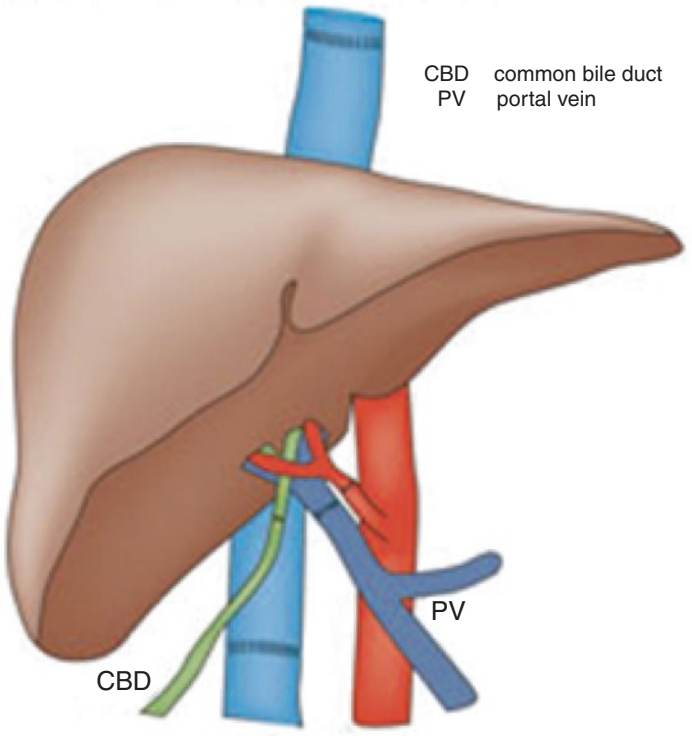

Figure 17.2 Conventional transplant technique

caval reconstruction involves the removal of the recipient's IVC and vascular reconstruction with end-to-end anastomosis between the donor's IVC and the recipient infra and suprahepatic IVC (Fig. 17.2). The piggy-back technique is associated with less transfusion requirements, shorter warm ischemia time and less use of veno-venous bypass. Once vascular anastomoses are completed the preservation fluid is flushed out of the graft and the blood supply opened to the new liver. The bile duct reconstruction can be performed by direct anastomosis or by an end-to-side Roux-en-Y choledocojejunostomy, used in recipients with a diseased or absent bile duct.

Post-transplant Care

The specific major concerns after LT are primary graft non-function, acute cellular rejection, vascular and biliary complications and infections (viral, bacterial and fungal). The time period following LT will aid in the differential diagnosis of these conditions (Table 17.3).

Table 17.3 Complications of liver transplantation according to time after transplant

First week	Primary graft non-function (1–2 days) Bile leaks—post-surgical Renal—acute kidney injury, calcineurin inhibitor (CNI) toxicity Pulmonary—pulmonary embolus, pneumonia CNS—seizures, headache, cerebrovascular accident
1–4 weeks	Acute cellular rejection (from 5 to 10 days) Cholestasis—Dug induced, ischaemic Hepatic artery thrombosis
5–12 weeks	Cytomegalovirus (CMV) hepatitis Acute cellular rejection Biliary complications—Ischaemic strictures, anastomotic stricture Hepatic artery thrombosis Hepatitis C recurrence
12 weeks to 6 months	Acute cellular rejection Biliary complications—Ischaemic strictures, anastomotic stricture Hepatitis B recurrence Epstein-Barr hepatitis Drug-related hepatitis
> 6 months	Ductopenic rejection EBV hepatitis Portal vein thrombosis Disease recurrence (HBV, HCV, tumours)

Primary Graft Non-function

Primary graft non-function occurs in 5% of LT and is associated with severe graft dysfunction manifested by hepatic coma, coagulopathy, jaundice, hypoglycaemia, renal dysfunction, lactic acidosis and hemodynamic instability. It is mainly related to a long cold and warm ischemia times and graft steatosis.

Acute Cellular Rejection (ACR)

ACR occurs in virtually all patients but is usually mild as the liver is considered a privileged organ with a higher resistance to immunological attack. Immunosuppression is usually started on the first post-operative day of liver transplant with methylprednisolone, in addition to oral immunosuppressants, most usually the calcineurin inhibitor tacrolimus. In patients with pre-existing renal dysfunction the use of renal sparing agents such as basiliximab is used early post-transplant to avoid the need for early exposure to Tacrolimus which can be nephrotoxic.

Acute or hepatocellular rejection requiring treatment escalation occurs usually after 5–20 days after LT in around 20% of patients. Clinical signs are non-specific and liver function tests lack specificity for the diagnosis (although a flare in ALT >100 IU/L, AST >100 IU/L, rising ALP or eosinophilia might be suggestive), so liver biopsy is mandatory for the diagnosis. The histological picture is the classic triad of portal inflammation, bile duct injury mediated by lymphocytes and venous endothelialitis. Increasing immunosuppression usually with high dose corticosteroids is the cornerstone of treatment and is effective in 90% of patients. In case of non-response further doses of corticosteroids or lymphocyte depleting antibodies may be needed to avoid chronic rejection and the need for re-transplantation.

Chronic or ductopenic rejection occurs in 2–5% of LT and is characterized by progressive loss of bile ducts and a cholestatic liver function tests. Liver biopsy is also needed for

diagnosis and depicts loss of interlobular and septal bile ducts in 50% of the portal tracts. Chronic rejection is usually irreversible. Notably, only <2% of grafts are now lost due to chronic rejection.

Post-transplantation Infections

Roughly 60% of LT experience an infection, a major cause of morbidity and mortality after LT. Infections that occur during the first month after LT are nosocomial infections related to surgery, including pneumonia, wound sepsis, liver abscess and biliary sepsis. In contrast, opportunist infections, such as CMV, and reactivation of latent infections occur 2–6 months after LT when the immunosuppression is its peak.

The infection prophylaxis protocols used in most transplant centres reflect this vulnerability to infection and include: surgical antibiotic prophylaxis, anti-viral agents against CMV and HSV, co-trimoxazole for Pneumocystis jirovecii (6–12 months) and fluconazole against Candida.

CMV infection is the most important opportunist infection. Risk factors are CMV positive donor in a CMV negative recipient, past acute rejection and intense immunosuppression. Patients present with a mononucleosis-like syndrome and the bone marrow, gastrointestinal tract, retina and liver may be involved. In some centres routine prophylaxis with oral valganciclovir is effective; however, there is concern with the emergence of resistant strains. Another strategy is to regularly determine CMV viraemia and start therapy if persistent or increasing viraemia occurs or when disease develops. Intravenous ganciclovir is reserved for patients with severe infections.

Vascular Complications

A routine US Doppler is performed in all transplanted patients on the first post-operative day to assess vascular anastomoses patency. Hepatic artery thrombosis has an inci-

dence of 1–7% and presents with graft dysfunction. Less commonly, it may be silent and present days to weeks later with ischaemic biliary lesions (ischaemic cholangiopathy) or recurrent bacteraemia and liver abscess. A Doppler ultrasound and/or CT scan is diagnostic. Therapeutic options include re-intervention and revascularization or re-transplantation. A hepatic artery stenosis results from anastomosis narrowing or kinking. A Doppler ultrasound will confirm the diagnosis and repair is surgical (if early in the post-operative course) or by angioplasty.

Reported portal vein thrombosis incidence is heterogeneous varying from 2.1% to 26%. It may present with graft dysfunction or ascites and bleeding due to portal hypertension. Surgical revision and thrombectomy may save the graft. If not, re-transplantation is necessary.

Biliary Complications

Post-surgical bile leaks are rare, occurring in 5% of LT. When they occur early (<30 days) they may present with localized/generalized peritonitis and/or biliary output from the drains. ERCP and plastic stent placement is the usual treatment; however, re-operation and surgical revision may be necessary. Anastomotic extrahepatic bile duct strictures have an incidence of 4–9% and usually present months after LT with intermittent fever, slow increase of bilirubin and an increase in alkaline phosphatase. It may be related to surgical technique, hepatic arterial problems and bile leaks. Magnetic resonance cholangiography allows the diagnosis. Treatment involves ERCP with balloon dilatation and/or plastic biliary stent placement which may need to be repeated. Resistant strictures may lead to the need for surgical biliary reconstruction. Ischaemic cholangiopathy results from progressive and indolent ischaemic damage of the bile ducts and resulting ischaemic strictures. Risk factors for this type of injury are AB0 incompatibility, prolonged cold ischemia time, hepatic artery thrombosis, rejection and DCD donors. Patients pres-

ent with pruritus and cholestasis, as well as recurrent cholangitis. Magnetic resonance cholangiography is useful to identify the typical beaded appearance produced by the intrahepatic strictures and narrowing of the donor common hepatic duct. ERCP with balloon dilatation or stenting may improve cholestasis and treat cholangitis if a dominant stenosis is identified. Hepato-jejunostomy or re-transplantation is the definitive treatment.

Long-Term Follow-Up

De novo malignancies and cardiovascular diseases are the major causes of death in the long-term largely due to the lifelong immunosuppression. In addition, disease recurrence in the graft should be monitored. The prevalence of metabolic syndrome is 50–60% in LT patients and there is a significant risk of cardiovascular events with an incidence of 10% at 5 years and 25% at 10 years. A regular assessment of cardiovascular risk and treatment of modifiable factors relating to obesity, diabetes mellitus, hypertension and dyslipidaemia are of paramount importance.

After LT there is an increased risk of malignancy, with reported incidences of 3–26% according to follow-up duration. Skin cancer, particularly non-melanoma, is the most frequent de novo cancer in this group and risk factors include: older age, chronic sun exposure and a prior history of skin cancer. Patients with a history of alcohol abuse and smoking are at increased risk of oesophageal, oropharyngeal-laryngeal and lung cancers. Lymphoproliferative disorders are also a concern, particularly in patients with positive EBV serology and under aggressive immunosuppression combinations. The tumour presents in lymph nodes or the graft and should be suspected in patients with fever, weight loss and night sweats even in the absence of lymphadenopathy since it can affect the graft. Treatment involves reducing immunosuppression. Systemic chemotherapy may improve survival and treatment with rituximab has improved prognosis. Finally, patients with

PSC and inflammatory bowel disease have an increased risk of colorectal cancer and should undergo an annual colonoscopy. Annual cancer screening protocols should be implemented to address these issues and advice given with regard to smoking cessation, sun avoidance, use of sun blocks and optimizing doses of immunosuppression.

Prognosis

Re-transplantation is necessary in 7–10% of patients due to graft loss. The main indications can be divided into early (e.g. primary graft non-function and hepatic artery thrombosis) and late (e.g. ischaemic cholangiopathy, ductopenic and recurrence of primary liver disease).

At 1 year after LT survival rates vary between 71% for ALF and 95% for elective indications. Ten years following LT survival is 48% for patients transplanted for malignant tumours and around 70% in patients transplanted for chronic liver disease, benign tumours and metabolic diseases.

Overall quality of life after LT is good in the majority of patients who return to normal social, familial and work activities. The advent of LT has been a major advance in the treatment of advanced liver disease and has revolutionized the survival prospects for these patients who would otherwise have been consigned to a premature death. The pioneering work of the surgeons, physicians and scientists who enabled this breakthrough must not be underestimated. Nevertheless, the burden of lifelong immunosuppression and their side effects can have an impact and should be sought in the clinic.

Case Study Answers

1. **Should this patient be referred for liver transplantation based on the severity of his liver disease?**

   In this case we have a patient with NASH cirrhosis who had three admissions for chronic encephalopathy despite medical therapy. An EEG supported the diagnosis of chronic hepatic encephalopathy and a head CT ruled out structural neurological disease. For this reason, although

his UKELD score was <49, the patient was referred for LT since he fulfilled the criteria for a variant syndrome.

2. **What aspects of the patient's medical history should be examined closely during transplant assessment?**

   The history of portal vein thrombosis (PVT) should be clarified. If it is an acute event and the patient is to be listed for LT, anticoagulation should be started. Conversely, PVT is not a contraindication, but is an important feature that will also impact the type of transplant surgery performed. An anastomosis between the donor portal vein and the recipient confluence of superior mesenteric vein or the use of a venous graft from the donor are possible options.

   The second factor to consider is the diagnosis of NASH cirrhosis that is usually associated with obesity, diabetes or metabolic syndrome. In this setting, a thorough cardiovascular assessment should include a cardiopulmonary exercise test to exclude ischaemic heart disease.

   Finally, the increased creatinine suggests the existence of renal dysfunction that should be investigated, with diabetic nephropathy considered in the differential diagnosis as this may be progressive after transplantation and may influence the choice and timing of the immunosuppressant regimen over the perioperative and early post-transplant period.

3. **Is the patients age a barrier to receiving a liver transplant?**

   Age is currently not a contraindication and the patient should be referred. However listing will depend on the pre-transplant evaluation and multidisciplinary team assessment of the individual case.

Bibliography

1. Starzl TE, Marchioro TL, Vonkaulla KN, Hermann G, Brittain RS, Waddell WR. Homotransplantation of the liver in humans. Surg Gynecol Obstet. 1963;117:659–76. PMID: 14100514; PMCID: PMC2634660.

2. Adam R, Karam V, Delvart V, O'Grady J, Mirza D, Klempnauer J, Castaing D, Neuhaus P, Jamieson N, Salizzoni M, Pollard S, Lerut J, Paul A, Garcia-Valdecasas JC, Rodríguez FS, Burroughs A. All contributing centers (www.eltr.org); European Liver and Intestine Transplant Association (ELITA). Evolution of indications and results of liver transplantation in Europe. A report from the European Liver Transplant Registry (ELTR). J Hepatol. 2012;57(3):675–88. https://doi.org/10.1016/j.jhep.2012.04.015. Epub 2012 May 16. PMID: 22609307.
3. Neuberger J, James O. Guidelines for selection of patients for liver transplantation in the era of donor-organ shortage. Lancet. 1999;354(9190):1636–9. https://doi.org/10.1016/S0140-6736(99)90002-8. PMID: 10560692.
4. Tschuor C, Ferrarese A, Kuemmerli C, Dutkowski P, Burra P, Clavien PA, Liver Allocation Study Group. Allocation of liver grafts worldwide—is there a best system? J Hepatol. 2019;71(4):707–18. https://doi.org/10.1016/j.jhep.2019.05.025. Epub 2019 Jun 12. PMID: 31199941.
5. Mergental H, Laing RW, Kirkham AJ, Perera MTPR, Boteon YL, Attard J, Barton D, Curbishley S, Wilkhu M, Neil DAH, Hübscher SG, Muiesan P, Isaac JR, Roberts KJ, Abradelo M, Schlegel A, Ferguson J, Cilliers H, Bion J, Adams DH, Morris C, Friend PJ, Yap C, Afford SC, Mirza DF. Transplantation of discarded livers following viability testing with normothermic machine perfusion. Nat Commun. 2020;11(1):2939. https://doi.org/10.1038/s41467-020-16251-3. PMID: 32546694; PMCID: PMC7298000.
6. ELTR. http://www.eltr.org/Overall-indication-and-results.html. Accessed 17 Oct 2021.
7. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med. 1996;334(11):693–9. https://doi.org/10.1056/NEJM199603143341104. PMID: 8594428.
8. Duvoux C, Roudot-Thoraval F, Decaens T, Pessione F, Badran H, Piardi T, Francoz C, Compagnon P, Vanlemmens C, Dumortier J, Dharancy S, Gugenheim J, Bernard PH, Adam R, Radenne S, Muscari F, Conti F, Hardwigsen J, Pageaux GP, Chazouillères O, Salame E, Hilleret MN, Lebray P, Abergel A, Debette-Gratien M, Kluger MD, Mallat A, Azoulay D, Cherqui D, Liver Transplantation French Study Group. Liver transplantation for hepatocellular carcinoma: a model including α-fetoprotein

improves the performance of Milan criteria. Gastroenterology. 2012;143(4):986–94.e3; quiz e14–5. https://doi.org/10.1053/j.gastro.2012.05.052. Epub 2012 Jun 29. PMID: 22750200.

9. Mathurin P, Moreno C, Samuel D, Dumortier J, Salleron J, Durand F, Castel H, Duhamel A, Pageaux GP, Leroy V, Dharancy S, Louvet A, Boleslawski E, Lucidi V, Gustot T, Francoz C, Letoublon C, Castaing D, Belghiti J, Donckier V, Pruvot FR, Duclos-Vallée JC. Early liver transplantation for severe alcoholic hepatitis. N Engl J Med. 2011;365(19):1790–800. https://doi.org/10.1056/NEJMoa1105703. PMID: 22070476.
10. Lee BP, Mehta N, Platt L, Gurakar A, Rice JP, Lucey MR, Im GY, Therapondos G, Han H, Victor DW, Fix OK, Dinges L, Dronamraju D, Hsu C, Voigt MD, Rinella ME, Maddur H, Eswaran S, Hause J, Foley D, Ghobrial RM, Dodge JL, Li Z, Terrault NA. Outcomes of early liver transplantation for patients with severe alcoholic hepatitis. Gastroenterology. 2018;155(2):422–30.e1. https://doi.org/10.1053/j.gastro.2018.04.009. Epub 2018 Apr 12. PMID: 29655837; PMCID: PMC6460480.