Liver Transplantation – What the Physician Should Know?

Amit Gupte¹, Akash Shukla²

Introduction

The first successful human liver transplantation (LT) in the world was reported by Sir Thomas Starzl in 1967.¹ In the following years, the results of liver transplantation were poor. Complex surgical procedure and nonselective immunosuppression made patients highly vulnerable to infections and the physicians had a daunting task of balancing this with the risk of rejection. With introduction of cyclosporine in 1979 by Calne² and tacrolimus in 1990 by Starzl³, outcomes steadily improved. Calcineurin inhibitors have remained the backbone of immunosuppressive regimens after liver transplantation. Improvement in surgical techniques, intensive care and immunosuppressive medications resulted in liver transplantation getting accepted as standard of care for end stage liver disease in 1983 in USA. The Human Organs Transplantation Act was passed in India in 1994 and first successful liver transplantation in India was reported in 1998.⁴ In western countries, majority of liver transplants are from a deceased donor (DDLT) while on the other hand liver transplants from living donors (LDLT) have expanded in Asian countries. In India transplant programs in north India do predominantly LDLT and those in south and west do a combination of DDLT and LDLT.⁵

Indications of a Liver Transplant

Liver transplantation is indicated for patients with cirrhosis of liver in whom, due to complications of cirrhosis, expected survival offered by liver transplantation would be greater than that due to natural progression of the disease.

End Stage Liver Disease

Hepatic decompensation, (ascites, jaundice, hepatic encephalopathy or variceal bleed) is an indicator of poor prognosis and indicates the possibility of LT being needed in the near future. Complications like spontaneous bacterial peritonitis (SBP), hepatopulmonary syndrome (HPS), hepatic encephalopathy (HE), porto-pulmonary hypertension (POPH) and hepatocellular carcinoma (HCC) herald a poor survival and evaluation for LT is recommended for these patients.

Scoring systems have been developed to assess the severity of liver disease and to stratify patients according to the likelihood of mortality. They have been used for organ allocation across the world. Model for End stage Liver Disease (MELD) score was devised in 2000 to predict the 3-month mortality in patients of liver cirrhosis undergoing transjugular intrahepatic portosystemic shunt (TIPSS) for variceal bleeding⁶ and was then proposed for prognostication of patients with end stage liver disease.⁷ It is a mathematical model comprising serum bilirubin, PT-INR and serum creatinine (MELD Score = 10 * [0.957 * ln(Creatinine)] + [0.378 * ln(Bilirubin)] + [1.12 * ln(INR)] + 6.43). Online calculators and applications are freely available for calculating the MELD score. A MELD score of > 15 has been recommended as an indication for liver transplantation.⁸ Recently, serum sodium has been included in the MELD score. However, the MELD score does not account for poor survival due to complications like HPS, POPH, refractory ascites, SBP, HE and HCC. Suitable patients with these complications should be considered for liver transplantation even when their MELD score is less than 15.

The Child-Turcotte-Pugh (CTP) score is a score based on serum bilirubin, serum albumin, severity of ascites, severity of encephalopathy and PT-INR. Patients of cirrhosis are classified in classes A, B or C as per CTP score 5-6, 7-9, 10-15 respectively. The 1-year survival of cirrhosis in Child A, B and C is 95%, 80% and 45% respectively and the 2-year survival is 90%, 70% and 38% respectively. A patient with CTP score > 7 i.e. Child B or C should be considered for LT.⁹ The counseling for liver transplant should start as soon as the first episode of hepatic decompensation (hepatic encephalopathy, ascites and variceal bleeding) occurs. Table 1 shows complications of liver cirrhosis and median survival of...
Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the most common primary malignant tumor of the liver. Liver transplantation for HCC provides widest possible resection margin as well as replace the cirrhotic liver with a normal one, thus treating the cause of HCC as well. In 1996, Mazzaferrro et al from Milan, reported a 4-year survival of 75% and a 4-year recurrence free survival of 83% for patients with HCC undergoing liver transplantation, when the tumor burden was a single lesion < 5cm or upto 3 lesions less than 3 cm each without macro vascular involvement or extra-hepatic spread.15 These selection criteria of patients with HCC for liver transplantation are known as the Milan Criteria. Patients of HCC within the Milan criteria are given additional MELD points in USA. In 2001, Yao et al showed that expansion of Milan criteria to single lesion < 6.5 cm and upto 3 lesions <4.5 cm with total tumor diameter <8 cm (UCSF criteria) resulted in similar survival and recurrence rates as the Milan criteria.16 The Milan and UCSF criteria have been developed for cadaveric organ allocation as a cadaveric organ is a public recourse. However organ from a living donor is not a public resource but a private gift to the patient. Hence many centers are using expanded criteria beyond UCSF for liver transplantation for HCC for LDLT. However as the number of lesions and size of lesions increase, the recurrence rate of HCC after transplantation increases. This has been described as a metro ticket concept. Hence, expansion of LDLT criteria for HCC has to be done very cautiously to prevent futile transplantations.

Table 1: Complications of liver cirrhosis and their median survival of patients16-14

<table>
<thead>
<tr>
<th>Complications of cirrhosis</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascites</td>
<td>20 months</td>
</tr>
<tr>
<td>Refractory ascites</td>
<td>6 months</td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td>6 - 9 months</td>
</tr>
<tr>
<td>Variceal bleed</td>
<td>Child A: 5 years</td>
</tr>
<tr>
<td></td>
<td>Child B: 3 years</td>
</tr>
<tr>
<td></td>
<td>Child C: 3 months</td>
</tr>
<tr>
<td>Hepato-renal syndrome</td>
<td>2 weeks</td>
</tr>
<tr>
<td>- type 1</td>
<td></td>
</tr>
<tr>
<td>Hepato-renal syndrome</td>
<td>6 months</td>
</tr>
<tr>
<td>- type 2</td>
<td></td>
</tr>
</tbody>
</table>

patients once these complications develop

Hepatocellular Carcinoma

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An important concern in patients of HCC on transplant waiting list is tumor progression beyond Milan criteria and subsequent dropout from the list. Hence it is strongly recommended that patients of HCC on waiting list be offered loco-regional bridging therapy if the expected waiting interval is more than 6 months.15

Hepatopulmonary Syndrome and Portopulmonary Hypertension

Hepatopulmonary syndrome (HPS) is a progressive complication of portal hypertension due to intrapulmonary vasodilatation of capillary and pre-capillary vessels. This results in rapid flow of inadequately oxygenated blood to the pulmonary veins in presence of preserved alveolar ventilation leading to ventilation-perfusion mismatch. Increase in endothelin-1 stimulates endothelial nitric oxide synthase (eNOS) via ET-B receptors and inducible nitric oxide synthase (iNOS) on monocytes, resulting in increase in nitric oxide (NO). This along with pulmonary vascular remodelling causes HPS.18

Diagnostic criteria of HPS include.18

1. Impaired oxygenation (PaO2< 80 mm Hg OR Increased age corrected alveolar-arterial oxygen gradient while breathing on room air)
2. Intrapulmonary vasodilation (confirmed by bubble contrast echocardiography or brain shunt fraction>6% by 99m Tc labeled macro aggregated albumin scan)
3. Liver disease (cirrhosis and/or portal hypertension)

HPS is found in 10-17 % of patients with cirrhosis.9 There is no definitive medical therapy for HPS. Liver transplantation is the only treatment that can reverse HPS. In a study from Mayo clinic patients of HPS, matched for severity who underwent transplant had a 5-year survival of 76% versus 23% in those who did not.20 Hence MELD exception points of 22 are given to patients with HPS with PaO2 <60 mm Hg.9 However patients of very severe HPS(PaO2 < 50 mmHg) have a high perioperative morbidity and mortality.21,22

Portopulmonary hypertension (POPH) is another pulmonary vascular complication of portal hypertension characterized by increased pulmonary vascular resistance due to endothelin 1 mediated vasoconstriction via ET-A receptors, resistance to NO mediated vasodilatation and pulmonary vascular remodeling.23 It is suspected on 2D-echocardiography by elevated pulmonary arterial systolic pressure. Diagnosis is confirmed by a right heart catheterization study showing elevated mean pulmonary arterial pressure (MPAP>25 mm Hg),increased pulmonary vascular resistance and normal pulmonary capillary wedge pressure.25 It has been demonstrated in 4.5 to 8.5% of liver transplant candidates.24 REVEAL registry demonstrated a 5-year survival of around 40% in patients of POPH.25 Severe POPH (MPAP>50 mmHg) is associated with increased mortality after liver transplantation and is considered a contraindication for LT.26 Medical therapy includes endothelin receptor antagonists, phosphodiesterase inhibitors and prostacyclines. MELD exception points are awarded to patients with moderate POPH (MPAP>35 mmHg) who achieve reduction in MPAP to <35 after medical treatment.23

Acute Liver Failure

Acute liver failure (ALF) is rapid development of severe liver dysfunction with encephalopathy and coagulopathy(PT-INR>1.5) in the absence of chronic liver disease.
Table 2: Common indications for liver transplant\textsuperscript{6,29}

<table>
<thead>
<tr>
<th>Acute liver failure (King’s College Criteria)</th>
<th>Acetaminophen-induced</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH &lt;7.3 or arterial lactate $&gt;3.0$ mmol/L after adequate fluid resuscitation OR any of the following</td>
<td>INR $&gt;3.5$</td>
</tr>
<tr>
<td>1. Jaundice $&gt;7$ days before encephalopathy</td>
<td>2. INR $&gt;3.5$</td>
</tr>
<tr>
<td>2. INR $&gt;6.5$ OR any 3 of the following</td>
<td>3. Serum bilirubin $&gt;17$ mg/dL</td>
</tr>
<tr>
<td>3. Serum creatinine $&gt;3.4$ mg/dL</td>
<td>4. Non-A, Non-B, drug-induced etiology</td>
</tr>
<tr>
<td>4. Non-Acetaminophen induced</td>
<td>5. Age $&lt;10$ or $&gt;40$ years</td>
</tr>
<tr>
<td>INR $&gt;6.5$</td>
<td>6. Non-Acetaminophen induced</td>
</tr>
<tr>
<td>Refractory ascites</td>
<td>7. INR $&gt;6.5$</td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td>8. INR $&gt;6.5$</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td><strong>Metabolic Disorders</strong></td>
</tr>
<tr>
<td>Refractory variceal bleed/Recurrent variceal bleed</td>
<td>LT is curative for some metabolic disorders like familial amyloidogenic polyneuropathy, primary hyperoxalosmia, etc. and is done even in presence of normal liver function.\textsuperscript{5}</td>
</tr>
<tr>
<td>Hepatopulmonary syndrome</td>
<td>A summary of common indications for liver transplant are mentioned in Table 2.</td>
</tr>
<tr>
<td>Portopulmonary hypertension</td>
<td><strong>Complications of cirrhosis</strong></td>
</tr>
<tr>
<td><strong>Metabolic conditions</strong></td>
<td>1. Severe cardiac or pulmonary disease</td>
</tr>
<tr>
<td>Familial amyloidosis</td>
<td>2. Uncontrolled AIDS</td>
</tr>
<tr>
<td>Glycogen storage disorder</td>
<td>3. Ongoing alcohol or illicit substance abuse</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>4. Hepatocellular carcinoma with metastatic spread</td>
</tr>
<tr>
<td>Primary hyperoxaluria</td>
<td>5. Uncontrolled sepsis</td>
</tr>
<tr>
<td>Patients diagnosed as ALF need rapid referral to transplant center for further assessment.\textsuperscript{6}</td>
<td>6. Intrahepatic Cholangiocarcinoma*</td>
</tr>
<tr>
<td>Patients fulfilling the Kings college criteria have poor transplant free survival (&lt;30%) and should be considered for urgent liver transplantation.\textsuperscript{27}</td>
<td>7. Extrahepatic malignancy</td>
</tr>
<tr>
<td>Intractable cerebral edema with cerebral perfusion pressure $&lt;40$ mmHg for more than 2 hours, evidence of irreversible neurological complications such as an intracerebral bleed, uncontrolled infection, high-dose multiple inotrope requirement are contraindications to LT.\textsuperscript{28}</td>
<td>8. Lack of adequate social support system</td>
</tr>
<tr>
<td>Late referrals for liver transplant result in many patients becoming ineligible for transplant itself as well as sub-optimal post-transplant outcome. Patients must be referred to a transplant centre as soon as they are diagnosed with ALF (Jaundice, Encephalopathy, INR $\geq 1.5$). The most common cause of ALF in India is acute viral hepatitis. Some etiologies like drug induced liver injury (DILI) and seronegative hepatitis have worse outcome than other etiologies. <strong>Contraindications for liver transplant</strong>\textsuperscript{6}</td>
<td>*Some centers do liver transplant for intra-hepatic cholangiocarcinoma after careful patient selection and after neo-adjuvant chemo-radiation therapy.</td>
</tr>
</tbody>
</table>

**Pre-transplant Evaluation of Recipient**

Once transplant is deemed necessary, prompt evaluation for transplant fitness of the recipient should be undertaken followed by enlisting. Initial process of pretransplant management focuses on etiological workup for liver disease, optimisation of medical therapy and identification and correction of reversible precipitating factors. A multidisciplinary approach centered around a hepatologist and including transplant surgeon, anesthetist, cardiologist, chest physician, infectious disease specialist, nephrologist, psychiatrist and a social worker is imperative.

1. **Cardiac evaluation:** A thorough cardiovascular risk stratification should be done in all LT candidates. All patients should be subjected to electrocardiography and a transthoracic echocardiography. Most patients would also be subjected to pharmacological stress testing (dobutamine stress test used commonly).\textsuperscript{16} When clinically indicated and when significant coronary artery disease is suspected or cannot be ruled out by above tests, a coronary angiography is performed.\textsuperscript{8} Advanced triple vessel disease is a contra-indication to liver transplant while significant coronary artery disease needs to be managed before patient undergoes liver transplant.

Hepatic imaging

Ultrasonography and Doppler study for patency of portal venous system should be done in all LT candidates. A triple phase cross sectional abdominal imaging (computed tomography or magnetic resonance imaging) is done for all patients to rule out the presence of HCC.\textsuperscript{8}
2. Pulmonary evaluation: A complete pulmonary evaluation including a chest X-ray, pulse oximetry and a pulmonary function testing should be done in all LT candidates. Patients with oxygen saturation on pulse oximetry less than 97%, should be subjected to a detailed workup for HPS including arterial blood gas analysis, bubble contrast echocardiography and a 99mTc labeled macro-aggregated albumin scan. Patients with hepatocellular carcinoma should be subjected to HRCT chest to evaluate for lung metastasis. All patients should undergo pulmonary function testing (PFT). A restrictive pattern on PFT has been shown to be associated with increased incidence of post-LT pneumonia, prolonged post-LT ventilator support and length of stay.30,31

3. Surgical evaluation: All LT candidates should be evaluated by a team of transplant surgeons with respect to portal vein patency, review of details of previous abdominal surgery and review of hepatic and biliary anatomy on imaging so as to identify challenges and potential technical difficulties likely to be encountered during transplant surgery.8

4. Nephrology evaluation: Acute kidney injury in patients of liver cirrhosis is defined as acute deterioration of renal function with an increase in serum creatinine of >50% from baseline, or a rise in serum creatinine of 0.3 mg/dl in <48 hours. Chronic renal disease is defined as an estimated glomerular filtration rate (GFR) of <60 mL/min calculated using the Modification of Diet in Renal Disease-6 formula for more than 3 months. The differential diagnosis of renal dysfunction in a patient of liver cirrhosis include intercurrent sepsis, hypovolemic, renal parenchymal disease and hepatorenal syndrome.32 All patients should be evaluated with routine urine examination, renal ultrasonography and GFR estimation.8 Patients of end stage liver disease with GFR<30 ml/min, with hepatorenal syndrome requiring more 8-12 weeks of renal replacement therapy and with renal biopsy showing >30% of glomerulosclerosis or fibrosis should be considered for simultaneous liver and kidney transplantation (SLKT).33

5. Dental evaluation: Dental caries are a potential focus of infection and sepsis in post transplant setting, dental assessment of all patients and treatment of caries or abscesses should be done prior to transplant.517

6. Infection screening: All LT candidates are screened for viral serology including Hepatitis A virus (HAV), Hepatitis B virus (HBV), Hepatitis C virus (HCV), HIV, Cytomegalovirus (CMV), Herpes simplex virus (HSV) and Epstein virus (EBV).8 Blood, urine and ascitic fluid cultures are to be done in all patients.

7. Vaccination: All LT candidates are usually vaccinated against pneumococcus, influenza, varicella, tetanus, Hepatitis A and Hepatitis B.17

8. Psychiatry and psychosocial assessment: All patients need psychiatry evaluation to uncover psychiatric illnesses, adjustment disorders and active substance abuse which may hamper the ability of the patient to comply with a complex medical regimen.8

9. Nutritional assessment: Malnutrition leads to poorer outcomes following transplantation. BMI less than 18.5 kg/m² and more than 40 kg/m² are predictors of death after liver transplantation.34 Due presence of ascites, edema and muscle wasting in patients with liver cirrhosis, patients may be nutritionally poor despite having a normal BMI. A study based on assessment of body composition using CT abdomen data, found that 56% of patients with liver cirrhosis with BMI >30 kg/m² actually had cachexia based on definitions by muscle mass.35 Hence detailed nutritional evaluation and consideration for enteral or parenteral nutrition support is recommended prior to LT.8

**Types of Transplant**

The two types of transplant are

1. Deceased donor liver transplant (DDLT): Liver is harvested from a deceased donor after brain death.

2. Living donor liver transplant (LDLT): Transplant is done using a part of the liver from a living donor (LDLT). As LT became the definitive treatment for end stage liver disease, the gap between demand and supply of organs widened and hence LDLT started becoming common especially in the east.

Split liver transplant: Split liver transplants is a unique type of cadaver transplant to increase the supply of donor organs. Whole liver graft from a cadaveric donor is split into a left lateral segment and a right extended graft which can be used for one pediatric and one adult liver transplantation respectively. In a study of 106 split liver transplant recipients, the 1-, 5-, and 10-year overall patient survival was 93%, 77%, and 73%, respectively in adults and 84%, 75%, and 69%, respectively in children.36

**Advantages and Disadvantages of DDLT/LDLT**

LDLT: LDLT is an elective surgery. The major advantage of LDLT is reduction of waiting time
mortality and a fully worked-up healthy donor. More liberal criteria for transplantation for HCC can be used in LDLT than DDLT. The main disadvantage of LDLT is donor risk of mortality and morbidity which is elaborated elsewhere in the text.

DDLT: DDLT is an operation that has to be performed immediately whenever a cadaver is available. LT recipients for DDLT have to be worked up and should be ready medically as well as mentally for the surgery. The major disadvantage of DDLT, especially in Asia is scarcity of organ donation and demand–supply mismatch. Long waiting times on DDLT amount to waiting list mortality and drop out.

**Cadaver Donors and Expanded Criteria Donors**

An ideal liver graft for DDLT is a whole liver fulfilling the criteria as per the Table 3.

It is desirable to have ideal liver donor for all liver transplants as it leads to reduced incidences of primary graft non-function, delayed graft function and peri-transplant morbidity and mortality. However, due to a huge discrepancy between demand and supply of liver grafts, livers from suboptimal donors are increasingly being accepted. These may pose a slightly higher risk of graft dysfunction and/or disease transmission to the recipient.

1. Older donor age: Liver grafts from older donors are at a higher risk of ischemia reperfusion injury, primary non function of the graft, hepatic artery thrombosis and higher rates of biliary complications. The outcomes can be improved by modifying other factors and recipient selection. In a study of 178 patients receiving livers from donors of at least 60 years of age, the 3-year survival was 76% when the cold ischemia time (CIT)(defined as time from flushing the portal vein in the donor to taking the liver out of the cold solution in which the graft was stored) was less than 7 hours.

2. Donation after cardiac death (DCD): DCD refers to retrieval of organs after circulatory arrest in the donor. This causes a period of hypoperfusion starting from the time of circulatory arrest–warm ischemia time. DCD recipients are likely to have higher incidence of biliary complications, ischemic cholangiopathy and primary graft non-function as compared to DBD recipients. However rapid surgical retrieval, selection of surgically straight-forward recipients and low risk recipients (age <60 years, serum creatinine<2mg/dl, not on ventilator support) have given outcomes comparable to DBD livers. However DCD donors are not presently used in India.

3. Steatosis: Macro-vesicular steatosis of > 30% in donor liver is a risk factor for poor graft function. Livers with macro-vesicular steatosis 30-60% can result in acceptable outcomes for properly selected donor-recipient combinations. Favorable donor factors are age < 40 years and CIT < 6hours and favorable recipient factors include age < 60 years, no prior abdominal surgeries and a low MELD score.

4. Hepatitis B core antibody (Anti HBc) positive donors: Livers from Anti HBc positive but HBsAg and HBV DNA negative donors can be used in patients with chronic hepatitis B who require Hepatitis B suppressive therapy post-transplant.

**Donor Evaluation for LDLT**

For LDLT, the donor is subjected to rigorous evaluation for a hepatectomy. This includes complete cardiovascular, hematological, psychiatry evaluation as well as complete hepatology evaluation including liver biochemistry, viral serology, ultrasonography, triple phase CT scan with volumetry and liver attenuation index (CTLAI) for steatosis and a magnetic resonance cholangio-pancreatography (MRCP). Normally mean attenuation of liver on CT abdomen is more than that of the spleen. CTLAI is the difference between mean liver attenuation and splenic attenuation. A value more than 5 indicates absence of steatosis. Liver biopsy should be done in obese donors as well as in donors having abnormalities on laboratory testing. A graft to recipient weight ratio of 0.8% is usually aimed at but not always achieved. A donor BMI >30 kg/m² is considered a relative contraindication for donor hepatectomy due to increased post-operative complications. Donor safety is of paramount importance.

**Risk to the Donor in LDLT**

The major disadvantage of LDLT is donor mortality and morbidity. Early donor death and acute liver failure can occur after LDLT. A systematic review looking at donor outcomes after LDLT reported a donor mortality of 0.2% and a median donor morbidity of 16%. Common complications reported include biliary leaks beyond postoperative day 7 (9%), bacterial infections (12%), incisional hernia (6%), pleural effusion requiring intervention (5%), neuropaxia (4%), re-exploration (3%), wound infections (3%), and intra-abdominal abscess (2%). Acute liver failure has been reported in 0.1% of the donors, more common among those who donated right lobe.
Long Term Outcomes in Donor in LDLT

Liver regeneration is rapid following living donor liver transplantation. Substantial hepatic growth occurs in the donor during the first month. An analysis of 487 donors showed that most laboratory values approached baseline levels within one year of donation, although platelet counts remained below pre-donation levels.

Surgical Techniques

1. DDLT: The first step in DDLT is organ procurement from the deceased donor. In the recipient, total heptectomy is performed, which is followed by an an-hepatic phase before the graft is implanted. The whole liver graft from the donor is then implanted with sequential anastomosis of donor hepatic veins to recipient vena cava (piggy back technique), anastomosis of portal vein, hepatic artery and the bile duct.

2. LDLT: In the donor: For a right lobe LDLT, the right hepatic artery and right portal vein are first dissected, followed by the inferior vena cava to isolate the origin of the right hepatic vein. The middle hepatic vein is not dissected at many centres while others include it in the graft. The right bile duct is then isolated. The liver parenchyma is transected using an ultrasonic scalpel. The main vessels are then divided and the isolated right lobe is flushed with preservative solution.

In the recipient: Implantation in the recipient starts with end-to-end anastomosis of the donor and recipient right hepatic veins. A portoportal anastomosis is then made between the donor right portal vein and the portal vein of the recipient. The hepatic artery anastomosis is completed using micro vascular techniques. Next a duct-to-duct anastomosis is performed.

Immunosuppression after Liver Transplant

LT does not require human leukocyte antigen (HLA) matching between and the recipient. Immune responses in the liver are skewed towards tolerance, making the liver a privileged organ. LT recipients need less intense immunosuppression than those of other solid organ transplants. The goal of immunosuppression after LT is to reduce allogeneic T-cell responses

Induction of Immunosuppression

Induction of immunosuppression refers to providing intense peri-operative immunosuppression to prevent acute cellular rejection. Corticosteroids are the mainstay for immunosuppression induction. Intravenous corticosteroids, typically methyl-prednisolone 500-1000 mg is administered during surgery in the an-hepatic phase and continued for 3 days followed by oral steroids with rapid tapering to around 20 mg/day over a week and maintained in the regimen for 3-6 months post-transplant.

Other agents that can be used for induction immunosuppression are polyclonal antibodies like Anti-thymocyte globulin (ATG) and Interleukin receptor 2 antibodies like basiliximab and daclizumab but their use is extremely rare.

Maintenance of Immunosuppression

The calcineurin inhibitors (CNIs) are the backbone of maintenance immunosuppressive regimen. The CNIs (Tacrolimus and Cyclosporine) act by inhibiting T cell activation by binding to specific receptors and blocking calcineurin which is a calcium dependent phosphatase within the cells. Tacrolimus is superior to cyclosporine with respect to incidence of acute cellular rejections, steroid resistant rejection episodes, better graft and patient survival after LT.

Tacrolimus is usually started at dose of 0.1 to 0.15 mg/kg in two divided doses on 1st to 4th day after LT. The dose is adjusted to achieve a desired trough level. Desired trough levels are 8-10 ng/ml in the first three post-transplant months and 6-8 ng/ml thereafter till 1 year. Beyond one year levels between 4-6 ng/ml usually suffice. A sustained release preparation of tacrolimus is also available for once a day dosing during maintenance immunosuppression.

CNIs cause afferent arteriolar vasoconstriction, tubular damage which is reversible early but may progress to chronic renal insufficiency. Other adverse effects of CNIs include hypertension, neurotoxicity, hyper-lipidemia and diabetes. Cyclosporine can cause gum hyperplasia and hirsuitism. Antimetabolites like mycophenolate mofetil and azathioprine are useful adjunctive maintenance immunosuppressive drugs that help to reduce CNI doses in setting of adverse events without increasing the risk of rejection episodes and are given usually for a year after LT.

Other adjunctive drugs are mTOR inhibitors like sirolimus and everolimus, but their use should be avoided in the first few months after LT as they interfere with wound healing and increased incidence of hepatic artery thrombosis was reported with early use of sirolimus. Some common drug interactions of immunosuppressive drugs essential to know are shown in table 4

Surgical Complications following Liver Transplantation

Hepatic artery thrombosis: Hepatic artery thrombosis (HAT) is the most serious vascular complication of LT and occurs in 2-7% of the patients after liver transplantation and the reported graft survival is as low as 27% at
of DCD livers, about 15-37%.57 Particularly common in recipients are recurrent strictures.17 Surgical endoscopic therapy those with patients who do not respond to balloon dilatation of stricture. Hepatico-jejunostomy is done for transhepatic cholangiography and cholangiography or percutaneous treatment is endoscopic retrograde technique.58 The conventional treatment is endoscopic retrograde cholangiography or percutaneous transhepatic cholangiography and balloon dilatation of stricture. Hepatico-jejunostomy is done for patients who do not respond to endoscopic therapy those with recurrent strictures.17 Surgical complications are summarised in Table 5.

### Infectious Complications

Infections are a major cause for post-transplant morbidity and mortality. In the first month after LT, nosocomial infections related to the surgery are common. From 2 to 6 months after transplant opportunistic infections and activation of latent infections is a major issue. After 6 months of transplant, community acquired infections predominate.17 Prophylaxis for CMV infection should be given for at least 3 months to all CMV seronegative patients who have received a graft from CMV positive donors. Oral prophylaxis for candida infection in first months is given in some centres. Some centres use trimethoprim-sulphmethoxazole for pneumocystis prophylaxis for 6-12 months to high risk patients post liver transplant.17 All LT recipients should receive annual influenza vaccine after LT.51 Infections in post-transplant period are summarised in Table 6.

### Life Expectancy after Liver Transplantation

Improvement in the surgical technique, ICU care and immune suppression has resulted in excellent short and long term survivals. Western literature reports 1 year and 10 year survival of upto 96% and 71% after LT.59 In India reported survival is 85% at 5 years.60 About 50% of the cases can be treated with re-intervention and re-vascularisation and the rest require re-transplantation.17

Ischemic bile duct injury: Ischemic bile duct injury can be due to ABO incompatibility, HAT and ischemia reperfusion injury.16 It is particularly common in recipients of DCD livers, about 15-37%.57

Anastomotic biliary stricture: The reported incidence of anastomotic stricture is about 4-9% and is related to suboptimal surgery technique.58 The conventional treatment is endoscopic retrograde cholangiography or percutaneous transhepatic cholangiography and balloon dilatation of stricture. Hepatico-jejunostomy is done for patients who do not respond to endoscopic therapy those with recurrent strictures.17 Surgical complications are summarised in Table 5.

### Table 4: Drug interactions of immunosuressive drugs55

<table>
<thead>
<tr>
<th>Class</th>
<th>CNIs</th>
<th>mTOR inhibitors</th>
<th>Mycophenolate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluroquinolones</td>
<td>Increased levels</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Macrolides</td>
<td>Increased levels</td>
<td>Increased levels</td>
<td>-</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Decreased levels</td>
<td>Decreased levels</td>
<td>Increased myelosuppression</td>
</tr>
<tr>
<td>Linezolid</td>
<td></td>
<td>Increased myelosuppression</td>
<td>myelosuppression</td>
</tr>
<tr>
<td>Triazoles</td>
<td>Increased levels</td>
<td>Increased</td>
<td>Increased myelosuppression</td>
</tr>
<tr>
<td>Ganciclovir, Valganciclovir</td>
<td>-</td>
<td>Increased</td>
<td>Increased myelosuppression</td>
</tr>
</tbody>
</table>

### Table 5: Surgical complications of liver transplantation17

<table>
<thead>
<tr>
<th>Complication</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular complications</td>
<td></td>
</tr>
<tr>
<td>Hepatic artery thrombosis 1-7%</td>
<td></td>
</tr>
<tr>
<td>IVC anastomosis stenosis 1-6%</td>
<td></td>
</tr>
<tr>
<td>Portal vein thrombosis 2-26%</td>
<td></td>
</tr>
<tr>
<td>Biliary tract complications</td>
<td></td>
</tr>
<tr>
<td>Biliary leakage 5%</td>
<td></td>
</tr>
<tr>
<td>Ischemic bile duct injuries 15-37% of patients receiving DCD grafts</td>
<td></td>
</tr>
<tr>
<td>Anastomotic biliary strictures 4-9%</td>
<td></td>
</tr>
</tbody>
</table>

### Late surgical complications: Incisional hernia

### Table 6: Infectious complications of liver transplant51

<table>
<thead>
<tr>
<th>Time after transplant</th>
<th>Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>First month after transplant</td>
<td>Nosocomial infections related to surgery and post-operative care</td>
</tr>
<tr>
<td>2-6 months after transplant</td>
<td>Opportunistic infections Viral-CMV, HSV&lt;EBV</td>
</tr>
<tr>
<td>More than 6 months after transplant</td>
<td>Community-acquired infections like enteric Gram-negative bacterial infections, Streptococcus pneumonia and respiratory viruses</td>
</tr>
</tbody>
</table>

### Disease and renal failure are the leading non-hepatic causes of morbidity and mortality after LT.55

### Health Promotion and Maintenance following LT

#### Obesity

New onset obesity may develop in up to 20% patients in the first 2-3 years after LT.62,63 With rising incidence of Non Alcoholic Steatohepatitis (NASH) as an indication for liver transplant, obesity after surgery will be a major concern. Dietary and nutritional counseling and regular exercises are integral to long term management of these patients. Bariatric surgery is being done for patients after liver transplant but has a higher morbidity and is technically more challenging.

#### Renal Impairment after LT

Regular monitoring of renal function using serum creatinine as well as estimation of urinary proteins is essential in LT recipients for an early recognition.
and appropriate management of renal failure. Blood pressure control (target of 130/80 mmHg) using calcium channel blockers or ACE inhibitors is appropriate. In the event of renal failure, withdrawal/reduction of CNI based immunosuppression is warranted and agents like sirolimus and everolimus are used along with antimetabolite drugs like mycophenolate.\textsuperscript{55}

**Diabetes Mellitus (DM)**

New onset DM is has been reported in upto 26% of all recipients.\textsuperscript{63} Diabetogenic factors after LT include corticosteroids, CNIs (tacrolimus>cyclosporine) and metabolic syndrome.\textsuperscript{55} The treatment of DM after LT should aim at HbA1c of <7% using lifestyle measures and pharmacotherapy as appropriate. When corticosteroids are being administered, insulin is the most effective and safe agent for glucose control but as steroids are stopped, patient can be shifted to oral drugs. Glucocorticoid induced transient diabetes is not uncommon after LT which abates with tapering off of the steroids. Metformin or sulfonylurea may be used in patients with normal renal function but sulfonylureas are preferred if renal function is impaired. In patient with controlled DM, tacrolimus may be changed to cyclosporine.

**Hypertension**

Hypertension can be seen in upto half of the patients after liver transplant. Calcium channel blockers like amlodipine are first line though verapamil and diltiazem are best avoided due to their interaction with CNIs. Beta-blockers are equally effective but carvedilol is to be avoided as it increases levels of CNIs. ACE inhibitors, Angiotensin receptor blockers are preferred in patients with DM, CKD and/or proteinurea.

**Dyslipidemia**

Dyslipidemia may occur in upto 70% of LT recipients.\textsuperscript{55} Apart from age, body mass index and genetics, medications – (CNIs, mTOR inhibitors and glucocorticoids) are major causes of dyslipidemia.\textsuperscript{55} Assessment of fasting lipid profile is recommended in LT recipients annually. LDL cholesterol > 100 mg/dl requires treatment- life style changes and if not controlled, statins are recommended.\textsuperscript{59} Pravastatin and fluvastatin are preferred due to absence of interactions. Ezetimibe is useful 2nd line drug. Gemfibrozil and Fenofibrate have potential for nephrotoxicity with concomitant CNI. Bile acid sequestrants decrease plasma mycophenolate level by 1/3rd and is best avoided. mTOR inhibitors are avoided in patients in severe hyperlipidemia.

**Malignancies**

LT recipients have higher risk of malignancies than non transplant population. Common cancers include skin cancer, oropharyngeal cancer, lung cancer, colorectal cancer and kidney cancer. Patients transplanted for HCC are at recurrence of HCC after LT.\textsuperscript{55} Any fresh skin lesions should be evaluated by dermatologist. mTOR based immunosuppression should be considered for patients transplanted for HCC and they should undergo abdominal imaging every 6 months. Patients with PSC and inflammatory bowel disease should undergo annual colonoscopy.\textsuperscript{55}

**Reproductive health**

Menstruation and fertility return to near normal in 90% of women. Conception should be planned in patients at 1 year after liver transplant with stable allograft function will controlled to morbidities and low maintenance immunosuppression. Prednisone and CNI appear to be safe during pregnancy.

**Re-transplantation**

Graft loss occurs in upto 7-10% of adults after liver transplantation, due to various reasons like HAT and primary non-function which cause early graft loss and ischemic cholangiopathy, recurrence of primary liver disease and chronic rejection which cause late graft loss.\textsuperscript{17} Liver re-transplantation is the only suitable therapy available for these patients. However re-transplant carries a higher morbidity and mortality as compared to a primary transplant.\textsuperscript{66}

**Conclusions**

1. LT is the only definitive treatment for appropriately selected patients with acute liver failure and cirrhosis.
2. Counseling and evaluation for LT should begin at the first sign of hepatic decompensation in patient with cirrhosis.
3. Conditions like HCC, HPS, POPH, intractable pruritis in PBC, recurrent cholangitis in PSC warrant LT even when cirrhosis may not be advanced.
4. A complete multidisciplinary pre-transplant evaluation is undertaken guided by the hepatologist.
5. LT is of two types: LDLT and LDLT; both having their own advantages and disadvantages.
6. Common causes of peri-transplant mortality are infections and surgical issues.
7. Liver requires lower degree of immunosuppression as compared to other organs.
8. Immun suppressive medications have many metabolic adverse effects as well as drug interactions that every physician should be watchful for.
9. Cardiovascular disease and renal failure are major causes of mortality and morbidity in LT recipients beyond 1 year of transplant and can be reduced by active surveillance and timely intervention.
10. Long term survivals (>10yrs) after LT are excellent (>70%) with appropriate care.


