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Liver Transplantation –Things To Remember

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I. Introduction

Patients with chronic liver disease and certain patients with acute liver failure require liver transplantation as a life-saving measure. The first successful human liver transplantation (LT) in the world was reported by Sir Thomas Starzl in 1967**[1]**. Since then Liver transplantation has undergone major improvements, with better selection of candidates for transplantation and allocation of scarce deceased donor organs (according to more objective criteria). Living donor liver transplantation came into existence to overcome the shortage of donor organs especially in countries where there was virtually no deceased donor programme. Advances in the technical aspects of the procedure, the intraoperative and postoperative care of both recipients and donors, coupled with the introduction of better immunosuppression protocols, have led to graft and patient survivals of over 90% in most high volume centres. The Human Organ Transplantation Act was passed in India in 1994 and first successful liver transplantation in India was done in 1998**[2]**. After that it is being done frequently.

Indication Of Liver Transplantation

Indications for liver transplantation are manifold and can be classified into end-stage liver disease, acute liver failure, and certain benign and malignant liver tumors.Liver transplantation should be considered for any patient in whom anticipated overall survival exceeds life expectancy of the underlying disease or where a significant increase in quality of life can be achieved.

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), hepato-pulmonary syndrome (HPS), porto-pulmonary hypertension (POPH), hepatic encephalopathy (HE) and hepatocellular carcinoma (HCC) herald a poor survival and evalution for LT is recommended for these patients as soon as possible.Scoring system have been developed to assess the severity of liver disease and to stratify patients according to the likelihood of mortality. Child-Turcotte-Pugh (CTP) classification (Figure 1) can be used to predict short term prognosis in patient awaiting transplantation. Patients of cirrhosis are classified in classes A, B and C as per CTP score of 5-6, 7-9 and 10-15 respectively and have an estimated 1 year survival of 95%, 80% and 45% respectively. Child B and C should be considered for LT3.Model for End stage Liver Disease (MELD) score was devised in 20004 and is a mathematical model comprising serum bilirubin, PT-INR and serum creatinine.

MELD = 3.78×ln[serum bilirubin (mg/dL)] + 11.2×ln[INR] + 9.57×ln[serum creatinine (mg/dL)] + 6.43. Online calculators are freely available for calculating the MELD Score. A MELD Score >15 has been recommended as an indication for LT5. However MELD Score does not account for poor survival due to complications like SBP, HE and HCC. Suitable patients with these complications should be considered for LT even when their MELD score is less than15.

Hepatocellular Carcinoma

Liver transplantation has become the mainstay of treatment for HCC in the early stages, as it offers the advantage of not only being curative, thus, minimizing the risk of recurrence; it also takes care of the complications associated with the underlying cirrhosis. There have been several criteria for listing these patients for transplantation. The Milan criteria defines early stage HCC as those with a single lesion < 5 cm, or no more than 3 lesions, with none > than 3 cm, in the absence of vascular invasion and metastases6. However, using the University of California, San Francisco, (UCSF) criteria (a single lesion ≤6.5 cm or 3 or fewer lesions with the largest being ≤4.5 cm and a total tumour burden of 8 cm or less), patients had a similar outcome following transplantation compared to those within the Milan criteria7. The MELD score in patients with HCC might be low, and this might prevent these patients from being given priority or even being listed in spite of the fact that their disease is fatal if left untreated.

Alcoholic Liver Disease (ALD)

A patient with ALD who is abstinent for a period of at least 3–6 months and who has had an evaluation with a psychiatrist is listed for transplantation if he has a CTP score of ≥7, portal hypertensive bleed, or an episode of spontaneous bacterial peritonitis8. A period of abstinence is mandatory to ensure that they do not relapse and also to give a trial of an alcohol-free period during which the liver function might recover.Acute alcoholic hepatitis (AAH) is a contra-indication for liver transplantation as the required period of abstinence is lacking. The severity of AAH is assessed using the Maddrey discriminant function (DF) score which predicts the risk of early death. Patients with a DF score of ≥32 are put on medical therapy.9

Cholestatic Liver Disease

The severity of cholestatic liver diseases such as primary biliary cirrhosis(PBC) and primary sclerosing cholangitis (PSC) is taken into consideration apart from using the child's score (≥7) as these conditions have more than 10% mortality at one year without transplantation[10]. Quality of life issues like recurrent cholangitis requiring repeated drainage procedures (endoscopic or percutaneous), intractable itching, xanthomatous neuropathy, and severe metabolic bone disease are some of the other indications for transplantation.

Acute Liver Failure

Acute liver failure (ALF) is rapid development of severe liver dysfunction with encephalopathy and coagulopathy (PT-INR>1.5) in absence of chronic liver disease. Patients diagnosed as ALF need rapid referral to transplant center for further assessment[5]. Patients fulfilling the Kings college criteria have poor transplant free survival (30%) and should be considered for urgent liver transplantation[12]. Intractable cerebral edema with cerebral perfusion pressure <40 mmHg for more than 2 hours and evidence of irreversible neurological complications are contraindications to LT[13]. Late referral for liver transplant result in many patients becoming ineligible for transplant itself as well as sub-optimal post transplant outcome. The most common cause of ALF in India is active viral hepatitis. Some etiologies like drug induced liver injury (DILI) and seronegative hepatitis have worse outcome than other etiologies.

Metabolic Liver Disease

Metabolic liver diseases which cause decompensation and irreversible damage are indications for transplantation. These include Wilson's disease, hereditary haemochromatosis, and α_1-antitrypsin disease. They also affect other organ systems; hence, pretransplant evaluation includes assessment of the concerned system to rule out systemic disease which would otherwise preclude transplantation.

Hepatopulmonary Syndrome And Portopulmonary Hypertension

Hepatopulmonary syndrome (HPS) is a progressive complication of portal hypertension due to intrapulmonary vasodilatation of capillaries 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 vasculatar remodeling causes HPS[14]. HPS is found in 10-17% of patients with cirrhosis. There is no definite medical therapy for HPS. Liver transplantation is the only treatment that can reverse HPS. However patients of very severe HPS (PaO2<50mmHg) have high perioperative morbidity and mortality[15].

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[16]. REVEAL registry demonstrated a 5-year survival of around 40% in patients of POPH[17]. Severe POPH (MPAP>50mmHg) is associated with increase mortality after liver transplantation and is considered as a contraindication for LT.

Contraindications For Liver Transplantation5

- Severe cardiopulmonary disease
- Extrahepatic malignancy (oncologic criteria for cure not met)
- Active alcohol/substance abuse
- Acute alcoholic hepatitis
- Active infection/uncontrolled sepsis
- Lack of psychosocial support/inability to comply with medical treatment
- Brain death
- Uncontrolled AIDS

Pre-transplant Evaluation5

The pre-transplantation evaluation is focused on the assessment of operative risks, medical compliance, and co-morbid conditions that could affect patient and graft survival, especially in the context of immunosuppressive therapy. A multi-disciplinary selection committee including hepatologist, transplant surgeon, anesthetist, cardiologist, chest physician, nephrologist, psychiatrist and a social worker reviews the evaluations to determine if the patient is in need of liver transplant listing and is a viable candidate. Once approved, patients are listed on the donor organ waiting list based on their ABO blood type, with priority established by the MELD score, either natural or assigned, with the exception of patients with acute liver failure who demand the highest priority as Status 1. Financial Screening: Obtain medical insurance approval first for transplantevaluation.

Hepatology Evaluation:

Thorough history and physical examination, optimize management of liver condition.

Laboratory Testing:

Hepatic synthetic function, electrolytes, renal function, complete blood counts Viral hepatitis profiles (A,B,C,D) Serologic studies for herpesviruses: cytomegalovirus, Epstein-Barr virus, and herpes simplex virus Testing for HIV infection Screening for non-viral infections: syphilis, toxoplasmosis Screening for latent tuberculosis: QuantiFERON-TB Gold assay or purified protein dervivative skin test Markers for other causes of liver disease (e.g. ANA, ASMA, AMA, iron studies, etc).

Tumor markers (e.g. alpha-fetoprotein Urinalysis and urine drug screen, 24h urine for creatinine clearance

ABO-Rh blood typing.

Cardiopulmonary Evaluation:Obtain electrocardiography and echocardiography; if indicated, perform pulmonary function testing, cardiac stress testing, and cardiac catheterization. Abdominal Imaging: Evaluation of hepatic artery and portal vein anatomy and screening for hepatocellular carcinoma using dynamic contrast imaging (CT orMRI) or ultrasonography with Doppler. General Health Assessment: Chest radiograph, bone density assessment, dental evaluation, vaccinations, esophagogastroduodenoscopy, age or condition-appropriate cancer screening. Dietician Evaluation: Assess nutritional status and dietary recommendations Social Work Evaluation: Assess psychosocial status and address care support needs Psychiatry or Psychology Evaluation: Review history of psychiatric and/or substance abuse disorders, if present Anesthesia Evaluation: Review cardiopulmonary and anesthesia risks and history of complications Transplant Surgery Evaluation: Review technical aspects and risks of surgery

Types of Transplant18

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. 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.

Since Ldlt is an elective surgery, the major advantage of LDLT is reduction of waiting time mortality and a fully worked-up healthy donor. The main disadvantage of LDLT is donor risk of mortality and morbidity. Ddlt is an operation that has to be performed immediately whenever a cadaver is available. LT recipients for Ddlt have toworked up and should be ready medically as well as mentally for the surgery.

Ideal cadaver donor

- Age <40 years
- Trauma as the cause of death
- Donation after brain death
- No steatosis
- No chronic liver disease
- No transmissible disease

It is desirable tohave 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 mortility. However due to a huge discrepancy between demand and supply of liver grafts, liver from suboptimal donors are being increasing accepted.

1. **Older donor age:** This poses higher risk of ischemia reperfusion injury, hepatic artery thrombosis and higher rates of biliary complications19. The outcomes can be improved by modifying other factors and recipient selection.
2. **Steatosis:** Micro-vesicular steatosis of >30% in donor liver is a risk factor for poor graft function19.
3. Donation after cardiac death (DCD): DCD refers to retrieval of organs after circulatory arrest in the donor. This causes a period of hypoperfusionstrting 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- functional as compared to DBD recipients20. DCD donors are not presently used in India.
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 the patients with chronic hepatitis B who require Hepatitis B suppressive therapy post transplant.

Cost Involved In LT

In private sector cost of LT is about 18-30 lakh rupees and some hospitals in public sector like KEM Hospital, Mumbai and ILBS, New Delhi offer LT6-12 lakh rupees. The usual cost of medications after LT is around 10-15 thousands per month.

Liver Donor Requirements21

- Being in good health
- Having a blood type that matches or is compatible with the recipient's, although some centres now perform blood group incompatible transplants with special immuno suppression protocols
- Having a charitable desire of donation without financial motivation
- Being between 18 and 60 years old
- Being of similar or bigger size than the recipient
- Before one becomes a living donor, the donor must undergo testing to ensure that the individual is physically fit. Sometimes CT scans or MRIs are done to image the liver. In most cases, the work up is done in 2–3 weeks.

Immunosuppression After Liver Transplant

LT doesnot require human leukocyte antigen (HLA) matching between the recipients22. LT recipients need less intense immunosuppression than those of solid organ transplant. Induction immunosuppression Corticosteroids have been the mainstay for induction of immunosuppression since the first successful cases of solid organ transplantation. Typical dosage is 500 or 1000 mg of methylprednisolone iv for three days followed by tapering over the first week to relatively low doses, 10 to 20 mg daily, and are usually maintained in immunosuppression regimen at least for the first 3 to 6 month post transplant23. Antibody therapies have been combined with corticosteroids or used to facilitate “steroid-free” regimens. Alemtuzumab (campath-1H) is a humanized rat monoclonal antibody against CD52 receptors on peripheral mononuclear cells. It has a significant depleting effect on peripheral as well as lymph node lymphocytes. Further studies are required to address the risk benefit issues on use of these agent.

Maintenance immunosuppression

The calcineurin inhibitors (CNIs) are the main drugs for maintenance of immunosuppression. 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 a dose of 0.1 to 0.15 mg/kg in two divided doses on 1st to 4th day after surgery. The dose is adjusted to achieve a desired trough level of 8-10 ng/ml in the first three post transplant months and 6-8 ng/ml thereafter till one year. Beyond one year levels between 4-6ng/ml is sufficient23. Adjunctive medications are usually prescribed in addition to a CNI and include the antiproliferative agents MMF, AZA, and SRL.

Complications Following LT

Surgical complications of livertransplantation 24
Vascular complications Hepatic artery thrombosis 1-7%
IVC anastomosis stenosis 1-6%
Portal vein thrombosis 2-26%
Biliary tract complications
Biliary leakage 5%
Ischemic bile duct injuries 15-37% ofpatients receiving DCD grafts
Anastomotic biliary strictures 4-9%
Late surgical complications: Incisional hernia

Infectious complications of liver transplant 25
First month after transplant
Nosocomial infections related to surgery and post-operative care
2-6 months after transplant
Opportunistic infections
Viral-CMV, HSV<EBV
Fungal- Aspergillus, Cryptococcal
Bacteria- Nocardia, Listeria, Mycobacteria
More than 6 months after transplant
Community-acquired infections like enteric Gram-negative bacterial infections, Streptococcus pneumonia and respiratory viruses.

Post Operative Care And Health Promotion

While the patient recovers from the operation, the family should take the opportunity to learn about precautions to be taken after discharge, understand the schedule for testing and follow-up appointments, become familiar with medicines, learn about symptoms and signs of potential problems, and understand the mechanism used to contact the liver transplant team round the clock in case of urgent problems. 26,27
Renal Impairment after LT

Regular monitoring of renalfunction using serum creatinineas well as estimation of urinaryproteins is essential in LTrecipients. Blood pressurecontrol (target of 130/80 mmHg)using calcium channel blockersor ACE inhibitors is appropriate.In the event of renal failure,withdrawal / reduction of CNIbased immunosuppression iswarranted and agents like sirolimusand everolimus are used alongwith antimetabolite drugs likemycophenolate. 28 Diabetes Mellitus (DM) New onset DM is has beenreported in upto 26% of allrecipients.Thetreatment of DM after LT shouldaim at HbA1c of <7% using lifestylemeasures and pharmacotherapy asappropriate. When corticosteroidsare being administered, insulin isthe most effective and safe agentfor glucose control while glucocorticoid is being tapered. Metformin or sulfonylurea maybe used in patients with normalrenal function but sulfonylureasare preferred if renal function isimpaired. In patient with controlledDM, tacrolimus may be changed tocyclosporine.

Hypertension

Hypertension can be seen inupto half of the patients afterliver transplant. Calcium channelblockers like amlodepine arefirst line though verapamil anddiltiazem are best avoided dueto their interaction with CNIs.ACEinhibitors, Angiotensin receptorblockers are preferred in patientswith DM, CKD and/or proteinurea.
Dyslipidemia Dyslipidemia may occur in upto70% of LT recipients30. Apart fromage, body mass index and genetics, medicat ions – (CNIs, mTORinhibitors and glucocorticoids) aremajor causes of dyslipidemia28.Assessment of fasting lipid profileis recommended in LT recipientsannually. LDL cholesterol > 100mg/dl requires treatment- life stylechanges and if not controlled, statinsare recommended.Ezetimibeis useful 2nd line drug. Gemfibroziland Fenofibrates have potential fornephrotoxicity with concomitantCNI. mTORinhibitors are avoided in patientsin severe hyperlipidemia.

Malignancies LT recipients have higher risk ofmalignancies than non transplant population including skin cancer, oropharyngealcancer, lung cancer, colorectalcancer and kidney cancer. Patientstransplanted for HCC are at recurrence of HCC after LT28. Any fresh skin lesions shouldbe evaluated by dermatologist. Abdominalimaging should be performed every 6 months. Patientswith PSC and inflammatory boweldisease should undergo annualcolonoscopy28.

After a successful liver transplant, most people are able to go back to their normal daily activities and eat as they did before. Some medication may cause weight gain, others may cause diabetes or a rise in cholesterol. Meal planning and a balanced low-fat diet can help you remain healthy. Transplant patients have a tendency to gain weight because of their retention of water. They are advised to lower their intake of salt to reduce or eliminate this water retention.Most people can return to a normal sex life after liver transplantation. It is important for women to avoid becoming pregnant in the first year after transplantation.

II. Conclusions

There has been substantial progress in both liver surgery and liver transplantation owing to improved preoperative diagnosis and intraoperative and postoperative care. Factors that limit the achievement of curative tumor resection are the high morbidity and mortality rates associated with insufficient volume of the liver remnant. Many tumors that were previously considered to be unresectable are now amenable to complete resection through innovative strategies that make manipulation of the liver volume possible. Portal-vein embolization or ligation causes atrophy of the ipsilateralhemiliver and hypertrophy of the contralateral side. Portal-vein embolization appears to be particularly valuable in patients who have underlying liver disease. The

concomitant administration of chemotherapy may further decrease both the tumor load and postoperative recurrences.

The use of partial liver transplantation is also rapidly increasing, as transplantation surgeons and hepatologists attempt to overcome the worldwide shortage of organs available for transplantation. Unfortunately, there is still a need for a substantial graft volume to support life, which places healthy donors at substantial risk. In the future, the use of new drugs based on innovative experimental models, together with a better understanding of the pathways leading to liver regeneration, may permit a very small liver remnant to regenerate, resulting in safer surgery for living donors and for patients with large tumors.

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