CHAPTER

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Indications, Contraindications & Long Term Care in Liver Transplantation

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"Good surgeons know how to operate, better ones when to operate, and the best when not to operate"

INTRODUCTION

Liver transplantation (LT) is a widely accepted & standard lifesaving therapy foradvanced chronic liver disease and acute liver failure. Although, medical management provides a temporizing measure, unlike LT, it is not a definitive cure for the complications of end-stage liver disease (ESLD). Advances in surgical technique, anesthesiology, intensive care unit management and immunosuppression combined with the increased awareness of transplantation have allowed for excellent long-term success. This has in turn led to an exponential increase in the transplant candidates and recipients.

Unfortunately, livers remain a scarce resource, and the growth in the transplant waiting list far exceeds the supply of organs. Available organs must be distributed by a regulated and organized system in a fair and equitable manner, with the allocation system being based on the tenets of justice, utility, autonomy, benevolence and nonmalfeasance. It is hence vital to have a clear understanding of the indications and contraindications for LT to maximize appropriate use of this limited resource. It is also prudent to always remind oneself that these indications are dynamic and may keep changing with emerging data.

PRINCIPLES OF DEFINING INDICATIONS

Before listing the disease specific indications for LT, it is necessary to define the principles on which these indications need to be formulated. Selection is based primarily on risk of death without a transplant. Patients are considered for elective transplantation if they have an anticipated length of life or survival in theabsence of transplantation that is less than that obtained with a liver transplant; with no effective medical or surgical alternatives to transplantation. All patients selected for the elective adult liver transplant list must have a projected 5-yearsurvival after transplantation of >70%. Indications for LT are also based on the ability of transplantation to improve quality of life. An integral part of defining principles is that all patients need to be regularly reviewed to ensure that they continue to meet criteria andhave not improved or become too sick to benefit from transplantation.

In addition to lowered life expectancy, (anticipated length of life <18 months), and unacceptable quality of life, indications for elective paediatric transplantation includegrowth failure or impairment, reversible neuro-developmental impairment due to liver disease, and the likelihood of irreversible end organ damage in the absence of LT.

BROAD INDICATIONS FOR LT (TABLE 1)

These can be classified into those diseases which lead to chronic liver disease and those which result in acute liver failure. Other indications include early or late graft failure resulting from a myriad of causes including primary non function, hepatic artery thrombosis, chronic rejection or disease recurrence.

In Countries where objective scoring systems like MELD are used for allocation, the sickest get transplanted first. There are certain conditions where higher MELD points are awarded to those who would otherwise have a low calculated MELD. This is done by giving weightage to their pathology, which would have a high mortality rate without LT. These are classified as "MELD exceptions" and are awarded points, and reevaluated every 3 months. Conditions included in the MELD exceptions are hepatocellular carcinoma-within Milan Criteria (single tumour less than 5cm or 3 tumours each no more than 3 cm in size with an absence of macrovascular invasion and distant metastases), Hilar cholangiocarcinoma-postneoadjuvant therapy, cystic fibrosis, portopulmonary hypertension, familial amyloid polyneuropathy, hepatopulmonary syndrome and primary hyperoxaluria.

Indications for LT are mainly based on the DDLT-predominant healthcare system prevalent in the west. These data have justifiably been extrapolated to the LDLT setting. Due to the inherent difference in the donation, LDLT may have certain ethical barriers to overcome and the question of "double equipoise" (balance of risk-benefit between the donor and recipient) should always be kept in mind before recklessly expanding the indications for LT beyond the realm of DDLT.

Irrespective of etiology, many patients with cirrhosis in the absence of an index complication such as ascites or variceal hemorrhage will not develop hepatic decompensation; although patients with cirrhosis have diminished survival compared to the populationas a whole. It is vital to appreciate that the mererecognition of cirrhosis per se does not automatically indicate the need for LT. It is the occurrence of major complications which predict drastically decreased survival which shouldprompt discussion about a possible role for LT. Complications of ESLD include hepatic encephalopathy,

Table 1: Indications for Liver Transplantation		
Acute Liver Failure		
Chronic Liver Disease	Child pugh c	Variceal bleed
	Meld >15	Hepatopulmonary syndrome
	Portopulmonary hypertension	Hepatic encephalopathy
	Hepatorenal syndrome	Diuretic resistant ascites
	Spontaneous bacterial peritonitis	Hepatocellular carcinoma
Early Graft Failure	Primary nonfunction	
	Hepatic artery thrombosis	
Late Graft Failure	Chronic rejection	
	Biliary cirrhosis	
	Recurrent disease	

renal dysfunction, fluid overload, variceal bleed, refractory ascites, spontaneous bacterial peritonitis and hepatopulmonary syndrome (HPS) amongst others. LT offers a survival benefit in HPS, with 76% of LT recipients surviving 5 years compared to 26% of matched patients with equivalent severity of hypoxemia and liver disease who are not transplanted. The recognition of renal dysfunction in a patient with cirrhosis has a dramatic effect on prognosis, with a substantial increase in the risk of mortality. The risk of death increases 7-fold in patients with renal dysfunction, with 50% of patients with cirrhosis dying within a month of the onset of renal dysfunction. Patients with cirrhosis who develop SBP have a one year mortality of 60%, thus making even the index episode of SBP an indication for LT. Certain cholestatic pathologies like primary biliary cirrhosis, have specific validated objective scoring systems which help guide the clinician. Apart from these, subjective symptoms like intractable pruritus are also an indication for LT in these diseases.

Indications and listing of patients with acute liver failure follow well defined criteria, which include the validated King's college criteria, Clichy criteria and the ALFED criteria. There are country specific criteria for supra-urgent listing of patients, like the UNOS-status 1(USA), UK-allocation policy etc. All these criteria follow a common theme which include fulminant hepatic failure fulfilling the King's college hospital criteria, acute Wilson's disease or Budd-Chiari syndrome, post liver transplantation hepatic artery thrombosis within 3 weeks (UNOS-7 days), presence of primary nonfunction of the liver graft-defined by objective parameters within 7 days of LT, a live liver donor with who develops severe liver failure within 4 weeks of the donor operation. Supraurgent listing in children follows a slightly different schema with LT being offered to children under two years of age with INR >4 or grade 3-4 encephalopathy.

CONTRAINDICATIONS (TABLE 2)

Due to the ever increasing gap between supply and demand with regards to the liver graft, it is imperative that patients who are unlikely to benefit from LT not be offered a liver; this should be done in an objective and impartial manner. The decision not to transplant affect the patient, their family in an irreversibly emotional and life changing manner; a hard decision which the treating physician must take. Hence, contraindications for liver transplantation and the delisting criteria are as important as the indications for LT itself. They tend to be dynamic and different between centers, depending on local expertise and level of comfort. There are both absolute and relative contraindications.

There are general principles based on which LT may be contraindicated for a particular patient; exceptions to the rule always exist. If the prospective candidate wereto be found physiologically unfit or unlikely to survive the stress of the surgery (advanced cardiac or pulmonary disease), or if there was active sepsis; it would be imprudent to offer the patient LT. In patients with metastatic disease, where the survival after transplantation may be too short to justify the risks of transplantation, LT should not be offered. Other contraindications include states where the postoperative quality of life may be unacceptable to the patient, those with severe intractable depression. A more relative contraindication is when the surgical team deems the surgery technically impossible (extensive venous thromboses); this depends on the expertise of the team and can vary between centres. Another absolute contraindication is when the patient wishes to exercise his autonomy and does not want an operation or is likely to be noncompliant.

Absolute contraindications have certain objective criteria; exponential advances in healthcare have moved the goalpost, whichis likely to be pushed further. Contraindications include severe PH (MPAP> 50mmHg) where the post transplant mortality is close to 100%, recent myocardial infarction, FiO_2 ≥50% indicating ventilator dependence, PEEP > 10mmHg suggestive of ARDS, amongst others. Relative contraindications reflect the changing trends due to emerging data in this nascent medical field, a few of which include treated extrahepatic malignancy (> 2 year period from treatment), HIV, Age (> 75 years) and moderate Pulmonary hypertension (MPAP 35-50mmHg).

Table 2: Contraindications for Liver Transplantation	
Absolute	Compensated cirrhosis, CTP < 7
	Severe PH (MPAP> 50mmHg)
	Recent myocardial infarction
	FiO2 ≥50%- ventilator dependence
	PEEP > 10mmHg- ARDS
	Angiosarcoma
	Active substance abuse
	Uncontrolled extrahepatic infection
	Brain death
Relative	Treated Extrahepatic malignancy (>2 year period from treatment)
	Cholangiocarcinoma
	Technical /operative challenge
	Age > 75 years
	Mod Pulm-HT (MPAP 35-50mmHg)
	No psychosocial support
	Psychiatric illness

LONG TERM CARE

With continued surgical experience and advances in organ preservation, intraoperative and perioperative care, immunosuppression, graft monitoring, and transplant care protocols, the majority of adult and pediatric recipients now live 10 to 20 years following the transplant operation. Following LT, recipients have gone on to win Olympic medals, play professional soccer, and become ambassadors for organ donation and transplantation. However, as recipients return to their daily lives, they encounter significant challenges, including medical treatments and follow-up, immunosuppression medications and their side effects, difficulties with employment, and stressors in their interpersonal relationships.

As survival continues to improve, more attention is being paid to the patient's quality of life. Long-term survivors represent a novel patient population who require a multidisciplinary approach to optimize medical/surgical treatments, psychosocial issues, achievement of milestones (graduation, marriage, employment, family establishment), health-related quality of life (HRQOL), and further survival. Transition to successful employment requires recovery of functional status and strength, maintenance of attention and concentration, development of personal confidence in the recipient, and overcoming fears of infection or job discrimination related to the posttransplant status. In a 20-year follow-up study, 50% of pediatric LT survivors were working or were homemakers.

An"ideal LT survivor" is one with a stable first allograft function on monotherapy, normal growth, and absence of the most common complications of immunosuppression, a goal which every clinician works towards. Malignancy screening, optimal treatment of recurrent disease and adequate management of metabolic disease are the crucial strategies upon which a successful& robust post-LT care system is based on.

Recommendations include strict adherence to cancer screening regimens to compensate for the increased risk of certain malignancies. Improved risk factor management to reduce and prevent long term cardiovascular, metabolic and renal disease. Treatment of recurrent viral hepatitis to improve long-term graft and patient survival. Transplant recipients are at a higher risk of acquiring infections than healthy individuals; vaccination is therefore highly recommended, ideally before immunosuppression is started.

Despite the excellent outcomes of pregnancies after LT, these gestations are considered high risk and should be monitored and managed by an experienced team of maternal-fetal medicine specialists in concert with the patient's transplant physicians. Unusual transplant-related complications have been reported, including intestinal volvulus secondary to internal hernia and thrombosis of infrarenalaortohepatic graft due to compression from the gravid uterus. Therapeutic adjustments may also be necessary to accommodate pregnancy-related issues in transplant recipients. The use of oral contraceptives in LT recipients depends on allograft function and certain drugs may be contraindicated.

Paediatric LT recipients who transition to adult care share many similarities in care needs with adult populations, but important differences exist. Paediatric patients have a longer lifetime exposure to immunosuppressive treatments and resulting adverse effects than many adult recipients. As immunosuppression contributes to increased risks of malignancy, infection, renal disease and cardiovascular disease, an emphasis on the minimization of immunosuppression will have far-reaching beneficial consequences on the patient.

Children experience a significant improvement in social competence after LT; body weight, head circumference, and anthropometrics improve as well. Some children may experience academic and psychosocial disabilities. As children grow, they become more concerned about their own health and body image, and may experience less pleasure than ordinary teenagers, which may result in a poor relationship with peers. The support of the family and the transplant team play an important role in the patient's quality of life.In a particular study only one third of the 10-year survivors met the criteria for the ideal survivor and 23% of the children had repeated a grade or been held back.

Overall, compared to healthy peers, long-term survivors of pediatric LT have lower physical HRQOL, some physical disability, and less health care utilization. Some of these results stem from the ever-difficult transition from pediatric to adult transplant patient. This adolescent transition remains a critical period in the paediatric LT recipient's course and is associated with noncompliance(upto 45%), poor follow-up, and even graft dysfunction and loss. Although survival outcomes

for paediatric LT have remained consistently excellent, much progress can be made through further refinements and protocols optimizing posttransplant care, development and social support framework. Once they have transitioned into adulthood, similar issues of weight gain, hypertension and renal dysfunction can occur and will be treated as they would be in adults.

CONCLUSION

The ultimate goal of LT is to provide a survival benefit to those who need it most and to be able to provide this benefit to the most individuals possible. Identifying appropriate candidates for LT is a complex process that requires a multidisciplinary approach. Survival after liver transplantation has progressively improved, which has led to an expansion in the indications and contraindications for transplant. The methods and scoring systems for liver allocation have also evolved over time, reflecting advances in the understanding and ability to treat various disease processes.

Long-term survival following LT continue to improve. Tosustain this encouraging trend and maximize longevity, the effects of comorbidities and recurrent disease will need to be minimized. Dose-reductions of immunosuppressive agents, weight reduction and screening programmes for malignancies help prevent comorbidities. Continued studies on immune tolerance and immunosuppressionminimizing tactics may have great potential in reducing their adverse effects. In addition, further studies to define and fine tune exiting protocols are needed to ensure ongoing progress in extending the longevity and quality of liver of a LT recipient.