Liver Transplantation: what every physician should know

Dr Abhideep Chaudhary
Associte Professor & Consultant Surgeon
Surgical Gastroenterology and Liver Transplantation
Sir Ganga Ram Hospital
New Delhi
Human liver

Largest & Most massive internal organ

Position:
- Upper right part of abdomen behind ribs

Weighs: 1.2 to 1.5 kg

Performs > 500 different functions in body

Natural regeneration capacity due to hepatocyte function
- Long term repeated exposure however causes liver damage & may finally cause liver failure

http://www.liver.ca/Liver_Health/
If.....
the functioning of liver is inadequate to meet the requirement of body
What Happens When Liver Fails
Causes of Liver Cirrhosis

- **Acute Liver Failure**
- **Alcoholic cirrhosis**
  - Represents the most common cause of cirrhosis\(^5\)
  - Accounts for 40% of US deaths from cirrhosis\(^5\)
- **HCV**
  - HCV is the most frequent diagnosis in patients undergoing liver transplantation\(^1\)
  - Viral recurrence is nearly universal, with up to 30% of patients progressing to cirrhosis\(^1,2\)
- **HBV**
- **HCC**
  - Accounts for 90% of all liver cancers\(^3\)
  - Causes 50% to 70% of liver-related mortality among patients with cirrhosis\(^4\)
  - Incidence and mortality is rising\(^4\)

HCV = hepatitis C virus; HCC = hepatocellular carcinoma; HBV = hepatitis B virus


**Causes of cirrhosis**

- Viral hepatitis (40%)
- Unknown (7%)
- Primary biliary cirrhosis (10%)
- Autoimmune hepatitis (4%)
- Other causes (2%)
- Viral + alcoholic hepatitis (5%)
- Alcoholic hepatitis (32%)

Treatment of liver failure

- Portion of donor’s liver to be transplanted
- Donor’s liver transplanted in recipient
- Recipient’s liver removed

© Healthwise, Incorporated
HOMOTRANSPLANTATION OF THE LIVER IN HUMANS

Denver, Colorado

An ideal treatment for several kinds of liver disease would be removal of the diseased organ and orthotopic replacement with a hepatic homograft. Patients with primary carcinoma of the liver, congenital atresia of the bile ducts, and terminal cirrhosis would all be candidates. The application of such therapy depends, first, upon the employment of a satisfactory operative procedure and, second, upon the use of suitable measures to prevent the immunologic rejection of the graft.

1. 3 year old. EHBA. Died on table due to bleeding
2. 48 year old. Cirrhosis with primary hepatoma. Died D22. PTE
3. 67 year old. Intrahepatic ductal carcinoma. Died D7. PTE
Nothing we had done in advance could have prepared us for the enormity of the task. Several hours were required just to make the incision and enter the abdomen. Every piece of tissue that was cut contained the small veins under high pressure that had resulted from obstruction of the portal vein by the diseased liver. Inside the abdomen, Bennie’s liver was encased in scar tissue left over from operations performed shortly after his birth. His intestine and stomach were stuck to the liver in this mass of bloody scar. To make things worse, Bennie’s blood would not clot... he bled to death as we worked desperately to stop the hemorrhage. The operation could not be completed’.

Thomas Starzl – The puzzle People
Liver transplantation – story of remarkable achievement and ongoing challenges
Long-term survival of liver transplant recipients has become the rule rather than the exception.
Who needs a liver transplant?

- End Stage Liver Disease
- Fulminant Hepatic Failure
- Metabolic Disease without liver failure
- Malignancy
Acute Liver Failure
Chronic Liver Failure
Can a patient with alcoholic liver disease get a transplant?

- For those in whom prolonged abstinence and medical treatment fails to restore health, transplantation may be considered.
- Patients who continue to drink alcohol despite medical advice are not considered for transplantation.
Severe Alcoholic Stetohepatitis–What to do?

- Distinction has to be made between alcoholism & ALD
- LT ‘ultimate sobering operation’
Rescue Liver Transplantation for Severe Alcoholic Hepatitis: Arriving Where We Started?

In the United States in 2012, most transplant centers select ALD patients after evaluation by an addiction specialist but also require observation of an abstinence period, most commonly 6 months. In the United Kingdom, there is no mandatory time require-

- Post-transplant survival at 6 months 77.8% (vs 22.8% in medical treatment)
- Survival ALD cirrhosis vs non-ALD cirrhosis similar
- < 20% go back to alcohol abuse post-transplant

Hepatocellular carcinoma

- Regular screening – HCC risk – 3%/year

- UCSF criteria (a single tumor up to 6.5 cm, 2 tumors < 4.5 cm, or total tumor diameter 8 cm) – frequently used and have been validated; 5-yr rates of overall survival are comparable to Milan criteria.

- Downstaging with TACE/radiofrequency ablation
When to Consider Transplantation?

- Determine the need for transplant
- All forms of effective therapy should be explored
- Severity of liver disease & potential benefits of LT – Timing
- Assess whether patient is an appropriate candidate
Determining the need for transplant

CPT score

MELD score

Clinical Pointers
<table>
<thead>
<tr>
<th>CTP score</th>
<th>1 point</th>
<th>2 points</th>
<th>3 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin</td>
<td>&lt; 2</td>
<td>2 – 3</td>
<td>&gt; 3</td>
</tr>
<tr>
<td>Albumin</td>
<td>&gt; 3.5</td>
<td>2.8 – 3.5</td>
<td>&lt; 2.8</td>
</tr>
<tr>
<td>PT prolonged</td>
<td>&lt; 4 sec</td>
<td>4 – 6 sec</td>
<td>&gt; 6 sec</td>
</tr>
<tr>
<td>(OR) INR</td>
<td>&lt; 1.7</td>
<td>1.7 – 2.3</td>
<td>&gt; 2.3</td>
</tr>
<tr>
<td>Ascites</td>
<td>Absent</td>
<td>Slight</td>
<td>Moderate</td>
</tr>
<tr>
<td>H E</td>
<td>None</td>
<td>Grade I – II</td>
<td>Grade III – IV</td>
</tr>
</tbody>
</table>

CPT – A: 5 – 6 (Well Compensated)
CPT – B: 7 – 9 (Significant Functional Compromise)
CPT – C: 10–15 (Decompensated)
Pointers for liver transplant

- **Clinical Indications**
  - Refractory ascites
  - Spontaneous bacterial peritonitis
  - Recurrent or severe hepatic encephalopathy
  - Hepatorenal syndrome
  - Significant weakness, fatigue, or progressive malnutrition
  - Recurrent cholangitis or severe pruritus
  - Progressive bone disease

- **Biochemical Indications**
  - Serum albumin <3.0 g/dl
  - Serum INR>1.7
  - Serum bilirubin >2 mg/dl (>4 mg/dl for cholestatic disorders)
Probability of Death after 1\textsuperscript{st} Variceal Hemorrhage

Overall 1 yr survival : 60\%
Probability of Death after Complications of Ascites

A Gines
Gastroenterol 1993

Post Transplant 1 yr survival 85-90%
Probability of Dying after Decompensation

V Arroyo, J Colmenero J Hepatol 2003
Recommendations

1. Patients with cirrhosis should be referred for transplantation when they develop evidence of hepatic dysfunction (CTP $\geq 7$ and MELD $\geq 10$) or when they experience their first major complication (ascites, variceal bleeding, or hepatic encephalopathy) (II-3).

2. Children with chronic liver disease should be referred when they deviate from normal growth curves or develop evidence of hepatic dysfunction or portal hypertension (II-3).

3. Patients with type I hepatorenal syndrome should have an expedited referral for liver transplantation (II-3).

Liver Transplantation 2008
All forms of effective therapy should be explored

- When medical therapy is effective in stopping the progression of liver disease, transplantation may be avoided or delayed
Acute liver failure –

- Coagulopathy, INR > 1.5
- Any degree of mental alteration
- < 26 wks duration
- No pre-existing chronic liver disease

Polson & Lee, AASLD 2005
Difficult to predict which patients will recover spontaneously
Deterioration can occur suddenly
The chance of receiving a timely LT increases
Once brainstem herniation has occurred, patients are not salvageable by any means, including LT
The survival following liver transplantation for acute liver failure is about 90%
Acute Liver Failure - Prognostic Models

- Clichy criteria
- King’s College criteria
- MELD scoring
- APACHE
- Dhiman (PGI), 3 adverse CPI
- Acharya, age > 50, INR> 3.5, Bil> 40 mg/dl
Decision making triggers in patients with acute liver failure.

**PROCEED**

- Persistence of accepted criteria associated with a poor prognosis
- Absence of co-morbidity independent of acute liver failure that would impact on survival
- Absence of complications of acute liver failure associated with reduced survival
- Absence of psychosocial profile suggestive of poor adaptation of rigour of post-transplant survival

**WAIT**

- Patients showing sustained evidence of improvement of prognostic criteria in the absence of clinical deterioration
- Paracetamol induced acute liver failure patients who do not have grade 3 or 4 encephalopathy irrespective of severity of coagulopathy
- Patients with paracetamol induced acute liver failure and severe acidosis or elevated serum lactate that responds rapidly to resuscitative measures
- Most patients when the liver allocated is marginal, especially steatotic, non-ABO identical or split, ABO-incompatible or the donor is aged over 60 years

**STOP**

- Evidence of compromised brainstem function, especially fixed and dilated pupils
- Invasive fungal infection
- Rapidly escalating inotrope requirements
- Severe pancreatitis [usually in paracetamol-related ALF]
Timing of the transplant – can have a profound impact on outcome

MELD > 30/ multisystem complications of ESLD / Severe debilitation – Success decreases by 25–50%
When to Consider Transplantation?

- Determine the need for transplant
- All forms of effective therapy should be explored
- Severity of liver disease & potential benefits of LT – Timing
- Assess whether patient is an appropriate candidate
Systemic evaluation – why?

- Assess: General health
- Evaluate: Specific problems
  Related to liver disease
  Unrelated to liver disease

AIM

- Identify and stratify: Perioperative risk
- Estimate: Long term outcome
  (considering potential extra-hepatic co-morbidity)
Systemic evaluation – what?

- Cardiac
- Pulmonary
- Renal
- Metabolic
- Infectious disease
- Extra hepatic malignancy
- Dental
- Psychological
- Nutritional
When Not to Transplant

- Active addiction
- Sepsis
- Advanced HCC
- Extrahepatic Malignancy
- Not fit for transplant
Where does the liver come from?

- Donation after brain death
- Living related donor
Organ donation in India

- 1.3 billion population
- HOTA (Legal Act) since 1994
- Liver used in only 40–50%
- Donation < 0.03 per million (20–35 per million – west)
Till then …

Living related liver transplant
Who can be a living donor?

- Any person above the age of 18 years can legally donate his part of liver however in India as per Human Organ Act 1994, liver donation is restricted to family members (brother, sister, father, mother, son daughter) or close relatives (Uncle, aunt, cousin, brother-in-law, sister-in-law, grand parents)
- Medically the liver donor should be medically fit and psychologically sound
- Approval from independent Ethics Committee
Liver transplantation is possible due to the amazing regenerative capacity of human liver.

Both donor and recipient eventually lead normal lives post procedure.
When can donor resume work following a surgery?

- Donor usually discharged within 7–10 days
- Donor can resume his normal activity within 3–4 weeks and resume his job within 6 weeks time
- No special precautions are needed for donor after about 4–6 weeks and he lives a normal life thereafter
Most liver transplant recipients are able to return to a normal and healthy lifestyle.

Most report that they feel re-energized, have an improved quality of life and enjoy everyday activities once more.

Liver transplant recipients are able to participate in normal exercise after their recuperation and women are able to conceive and have normal post-transplant pregnancies and deliveries.
Will the patient have to depend on lots of medication for the rest of life?

- Patient needs medication to protect the new liver from rejection
- These medications however reduce both in dosage and number as time passes and the immune system gets used to the new liver
Immunosuppression

- Triple therapy
  - CNI + MMF + Steroid
- Steroid withdrawal –6 weeks– 3 mon
  - HCV – 6 mon
  - AIH
Issues after transplant

- *Infectious complications*
  - *Viral* – CMV, HSV, Varicella
  - Community Acquired

- *Immunosuppression and rejection*

- *Systemic Complications*
  - Cardiovascular, Diabetes, Obesity, Osteoporosis, Malignancy (PTLD)
  - Renal Dysfunction

- *Biliary Strictures*

- *Disease Recurrence*
  - HCV, HBV
  - Non viral disease recurrence
Complications of immunosuppression

- Nephrotoxicity
- Cardiovascular complications
- Risk of infection
- Risk of malignancy
Management

- Close monitoring of renal function
  - GFR, S Creatinine – mTOR
- Avoid nephrotoxic drugs
- Pre-LT or post-LT renal insufficiency – consider mTOR inhibitors or low dose CNI + MMF
- Early renal transplant when dialysis is imminent

Ojo et al New E J Med 2003
Hypertension after LT

- Hypertension occurs in 40–75%
  - Risk factors: medications (CNIs, steroids), renal failure, pre-existing HTN or obesity

- Management
  - Reduce calcineurin inhibitors or switch to mTOR inhibitors; discontinue steroids

- Medications
  - 1st 6 months: Ca channel blockers (amlodipine), alpha blockers (doxazosin), clonidine/ arkamin, ? Beta blockers
  - After 6 months: similar to non-transplant patients
    - ACE inhibitors and beta blocker

Hyperlipidemia after LT

- Very common: ~50% of LT recipients
  (Hypercholesterolemia in 16 to 43% and hypertriglyceridemia in 40 to 47%)
  - Risk factors: steroids, mTOR inhibitors, DM, pre-LT hyperlipidemia, obesity

- Management
  - Lifestyle modification: diet and exercise
  - Statins, avoid bile acid binding resins
  - Switch cyclosporine to tacrolimus; switch from mTOR inhibitors to tacrolimus

### Diabetes Mellitus in Liver Transplant Recipients

#### Pre-Tx DM and New Onset DM

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Pre-Tx DM (%)</th>
<th>New Onset DM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bigam 2000</td>
<td>278</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Al-Dossary 2002</td>
<td>177</td>
<td>8</td>
<td>17</td>
</tr>
<tr>
<td>Baid 2002</td>
<td>176</td>
<td>17 HCV</td>
<td>13 others</td>
</tr>
<tr>
<td>Steinmuller 2000</td>
<td>618</td>
<td>11</td>
<td>7.2</td>
</tr>
<tr>
<td>John 2003</td>
<td>291</td>
<td>19.6 HCV</td>
<td>16.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11.5 others</td>
<td>10.1</td>
</tr>
</tbody>
</table>

#### Body Mass Index

![Bar chart showing DM by Body Mass Index](chart.png)

**UNOS Scientific Registry: 1988-1996**

18-36% of all liver transplant recipients have either pre-existent or new onset diabetes mellitus.
~20% of late deaths caused by cardiovascular disease

Risk factors

- Uncontrollable factors
  - preexisting disease, male sex, family history, advanced age, immunosuppressive drugs

- Controllable
  - diabetes, obesity, hyperlipidemia, HTN
Management of CAD in Transplant Recipients

- **Changes in health style**
  - Smoking should be discouraged
  - Regular exercise
  - Weight management

- **Treatment of metabolic complications**
  - Hyperlipidemia, HTN & diabetes
  - Monitor Hb1Ac and urine micro albumin

- **Screening for CAD**
  - Exercise stress test & carotid duplex every 5 years
Bone Disease after OLT

● Risk factors
  ● Pre–LT bone disease (PBC or AIH treated with glucocorticoids, alcohol–related liver disease, immobility, vitamin D deficiency, steroids)
  ● BMD declines for 6 months because of steroids and then increases

● Management
  ● Bone densitometry baseline and every 2–yrs
  ● Calcium (1500mg/d), vitamin D (800 IU/d) and exercise
  ● Osteopenia or osteoporosis: bisphosphonates/calcitonin

Disease Recurrence

- ALD recidivism
- HCV progression
- HBV recurrence
- HCC recurrence
Long term care

- Malignancy, CAD, renal failure and recurrent disease are the most common causes of late mortality
- Management of HTN, DM, obesity, CAD, hyperlipidemia and osteoporosis is similar to that for general population
- Cancer screening/surveillance are important
- Long-term outcome is dependent on close supervision
Patients with cirrhosis should be referred for transplant if
- Childs ≥ 7
- MELD ≥ 10
- First major complication (Intractable ascites, HE, variceal bleed)

ALF – Early referral essential

HCC in cirrhosis with PHT have low recurrence rates if transplanted within criteria

Liver transplant 1 year survival ≥ 90%
Liver transplant complications cannot be totally prevented, but if the care provider knows how to avoid, identify, and treat these complications, liver transplant recipients will enjoy longer and more productive lives.
Patient selection and timing is key to success.
Don’t take me to heaven, no one needs me there!

Pledge your organs
Save a life

http://www.sgrh.com/onlinePledge.php
Tempora mutantur et nos mutamur in illis

"The times change, and we change with them"
Queries/Suggestions

Contact:
Dr Abhideep Chaudhary
Ph: +91-9871859776
drabhideep@yahoo.com
www.drabhideep.com