Liver Transplantation

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August 29, 2019
Transplant Hepatology
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Objectives

• Learn the common indications for liver transplant
• Learn when patients should be considered for a liver transplant
• Learn the pre-transplant assessment of patients
• Learn about the liver allograft allocation system and the challenges it poses to our patients
Liver Transplantation

• Dr. Thomas Starzl performed the first liver transplantation (LT) on March 1, 1963 on a 3-year-old boy with biliary atresia at the University of Colorado.
  • The child died during surgery because of coagulation disorder and uncontrolled bleeding.
  • Of the first 5 patients, none survived longer than 23 days due to ischemia-reperfusion injury and rejection.

• In 1967, with regular use of anti-thymocyte globulin, Dr. Starzl was able to perform the first successful LT series of 8 children.
  • The first case was a 19-month-old girl with hepatoblastoma who survived more than 1 year before dying of recurrence.

Timeline

- **1963**: First human liver transplant at University of Colorado
- **1967**: Cyclosporine introduced in liver transplantation
- **1979**: University of Wisconsin solution improves liver allograft preservation
- **1981**: First successful liver transplant at University of Colorado
- **1987**: 80% 1-year liver recipient survival with cyclosporine-prednisone
- **1989**: FK-506 (Tacrolimus) introduced in liver transplantation

2018 Worldwide Distribution of LT

~32,000 LT
2018 Transplants by Organ Type

- Kidney 21,167
- Liver 8,250
- Heart 3,408
- Lung 2,530
- Kidney/Pancreas 836
- Pancreas 192
- Intestine 104
- Heart/lung 32
- Vascular allograft 11

https://unos.org/data/transplant-trends/
Common Indications for LT in 2018 (8,250)

- Chronic Liver Disease (5,499)
- Acute Liver Failure (268)
- Neoplastic Liver Disease (1429)
- In-born Error of Metabolism (236)
Indications for LT

**Chronic Liver Disease**
- *Alcoholic Cirrhosis*
- *NASH*
- *Hepatitis C*
- *Hepatitis B*
- Autoimmune Hepatitis
- PSC
- PBC
- Cryptogenic

**Acute Liver Disease**
- *Alcoholic Hepatitis*
- *Acetaminophen*
- Viral Hepatitis
- Autoimmune Hepatitis
- PSC
- PBC
- Cryptogenic

**Neoplastic Liver Disease**
- *Hepatocellular Carcinoma (adults)*
- Cholangiocarcinoma (rare)
- Hepatoblastoma (children)
- Epithelioid Hemangioendothelioma (rare)
- Neuroendocrine Tumor (rare)
Questions when considering LT

1. Does the patient need a liver transplant?
2. Is the patient an appropriate liver transplant candidate?
3. How can we optimize the chance of the patient receiving a transplant?
Types and Stages of Liver Disease
Liver Injury

Acute

Resolution

Death or Liver Transplant

Acute Liver Failure

No cirrhosis

Cirrhosis

Compensated Cirrhosis

Death or Liver Transplant

Variceal Bleeding

Ascites

Hepatic Encephalopathy

HCC

Death or Liver Transplant
Who needs a liver transplant?

1. Increase survival
2. Improve symptoms
Grading System for Chronic Liver Disease

• CPT Score
• MELD Score
• MELD-Na Score
Childs-Pugh-Turcotte

- CPT score was first developed in 1964 to describe severity of liver disease
- Incorporates clinical findings and laboratory test results
- A-C
- Correlates with mortality
- Used in past to prioritize patients on liver transplant list
- Too subjective and relied too heavily on waiting time
### Childs-Pugh-Turcotte

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<tr>
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<tbody>
<tr>
<td>Hepatic encephalopathy</td>
<td>None</td>
<td>I-II</td>
<td>III-IV</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
<td>Moderate</td>
<td>Severe</td>
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<tr>
<td>Total bilirubin mg/dL</td>
<td>&lt;2</td>
<td>2-3</td>
<td>&gt;3</td>
</tr>
<tr>
<td>Albumin g/dL</td>
<td>&gt;3.5</td>
<td>2.8-3.5</td>
<td>&lt;2.8</td>
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<tr>
<td>INR</td>
<td>&lt;1.7</td>
<td>1.7-2.2</td>
<td>&gt;2.2</td>
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## Childs-Pugh-Turcotte

<table>
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<tr>
<th>Total Points</th>
<th>Class</th>
<th>Median Survival</th>
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<tbody>
<tr>
<td>5-6</td>
<td>A</td>
<td>10 years</td>
</tr>
<tr>
<td>7-9</td>
<td>B</td>
<td>5 years</td>
</tr>
<tr>
<td>10-15</td>
<td>C</td>
<td>2 years</td>
</tr>
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</table>
Model for End-Stage Liver Disease

- MELD developed in 2000 at the Mayo Clinic
- Total bilirubin, Creatinine, INR, and Sodium
- MELD = 10 * ((0.957 * ln(Creatinine)) + (0.378 * ln(Bilirubin)) + (1.12 * ln(INR))) + 6.43
- Predicts chance of death with cirrhosis
- Ranges from 6-40
Model for End-Stage Liver Disease

- Adopted by United Network for Organ Sharing (UNOS) in 2002 to prioritize position on liver transplant list
- No change in post-LT outcomes with higher pre-LT MELD score
- Miscellaneous uses
  - predicting perioperative risk for non-liver transplant surgery
  - mortality after TIPS

MELD-Na Score

• MELD-Na Score incorporates hyponatremia
  • Common in patients with cirrhosis
  • Serum sodium is a reflection of the degree of vasodilatory state in cirrhosis and predicts mortality independent of MELD score
  • 5% increase in mortality with each mmol decrease in serum sodium between 125mmol/L to 140mmol/L.

• In January 2016, UNOS replaced MELD score with MELD-Na score to prioritize patients on the liver transplant list

• Elevates the transplant priority in about 12% of listed patients

# Model for End-Stage Liver Disease

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<tr>
<th>MELD</th>
<th>Median Survival</th>
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<tr>
<td>6-10</td>
<td>&gt;5 years</td>
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<tr>
<td>11-17</td>
<td>21 months</td>
</tr>
<tr>
<td>18-24</td>
<td>5 months</td>
</tr>
<tr>
<td>25-40</td>
<td>69 days</td>
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## Typical Patient Characteristic Based on MELD

<table>
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<tr>
<th>MELD Score</th>
<th>Patient Characteristics</th>
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<tr>
<td>&lt; 10</td>
<td>At home: Indistinguishable from you or me</td>
</tr>
<tr>
<td>10-19</td>
<td>At home: early cirrhosis</td>
</tr>
<tr>
<td>20-29</td>
<td>May be hospitalized: jaundiced, may have ascites, some renal dysfunction</td>
</tr>
<tr>
<td>30-39</td>
<td>Typically hospitalized, may be in ICU: visibly jaundiced, large ascites, encephalopathic</td>
</tr>
<tr>
<td>40 or more</td>
<td>Typically in ICU on life support: intubated, renal replacement therapy, vasopressors</td>
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</tbody>
</table>
Three-Month Mortality Based on MELD

Mortality Risk of LT Based on MELD

Mortality Risk of LT Based on MELD

1-Year survival is superior with liver transplant in patients with MELD score greater than 15-17

Who needs a liver transplant?

1. Increase survival
   • Overall 1-year survival is 89% for LT
   • Overall 5-year patient survival is 75%
   • If patient has liver disease that’s helped with LT that has poorer outcomes than above, LT is indicated

2. Improve symptoms

Complications of Cirrhosis

- Decompensated cirrhosis
  - Ascites
  - Hepatic encephalopathy
  - Variceal bleeding
- Recurrent cholangitis – primary sclerosing cholangitis (PSC)
- Failure to thrive in polycystic liver/kidney disease (PCLKD) – sarcopenia
- Hepatopulmonary syndrome (HPS) – progressive hypoxia
- Portopulmonary syndrome (PPHTN) – progressive right heart failure
Liver Transplantation

• Need to take into consideration that LT is trading one disease (chronic liver disease) for another set of diseases (post-LT liver and systemic disease)

• New allograft is prone to rejection and subsequent dysfunction

• After LT, most will need life-long immunosuppression
Post-LT Complications

- Acute cellular rejection, chronic rejection, and humoral rejection
- Biliary strictures – anastomotic strictures, ischemic cholangiopathy
- Vascular problems – hepatic artery thrombosis, portal vein thrombosis, hepatic venous outflow stenosis
- Recurrence of primary liver disease
- Infections – bacterial, CMV, fungal infections, EBV, HEV
- Malignancy – skin cancer, PTLD,
- Metabolic syndrome – hypertension, DM/glucose intolerance, hyperlipidemia, obesity
- Bone disease – osteoporosis due to preexisting cholestatic disease, steroids, and calcineurin inhibitor (CNI) use
- Renal disease – combination of pre-existing renal disease, ATN during LT, development of DM/Htn, and chronic CNI use
Incidence of Chronic Renal Failure (GFR<30 or ESRD) after Nonrenal Transplantation

Pre-Transplant Evaluation

• Cardiopulmonary assessment
  • Echocardiogram to assess for wall-motion abnormality, LV/RV function, RV systolic pressure, and transpulmonary shunt
  • Coronary artery disease assessment in appropriate patient – stress test vs. left-heart catherization
  • ABG
  • PFT in appropriate patient

• Renal function
  • About 14% will have chronic renal failure (GFR<30 or ESRD) at 36 months
  • Simultaneous liver and kidney (SLK) transplant has better outcome than sequential liver and kidney transplant
  • 9.9% of adult LT was with SLK in 2016

Pre-Transplant Evaluation

• Malignancy – needs age appropriate screening
• Assessment of infectious risks with appropriate vaccination
  • HIV
  • TB
  • Fungal serologies
  • CMV/EBV status
• Surgical anatomy – need cross-sectional imaging
  • Vascular
  • Biliary
  • BMI > 40
• Functional status
  • Age
  • Sarcopenia
  • Frailty
• Psychosocial evaluation
  • Substance abuse history
  • Social and financial support
• Insurance

Contraindications to LT

- Cardiopulmonary disease that cannot be corrected (poor LV function, severe pulmHtn)
- AIDS
- Extrahepatic malignancy not meeting oncologic criteria for cure
- HCC with metastatic spread
- Intrahepatic cholangiocarcinoma
- Hemangiosarcoma
- Anatomic abnormalities that preclude liver transplantation
- Uncontrolled sepsis
- Acute liver failure with sustained intracranial pressure >50mmHg or cerebral perfusion pressure <40mmHg
- Persistent nonadherence with medical care
- Lack of social support

Adult Liver Allocation

• Adult Status 1a
  • Fulminant liver failure, hepatic artery thrombosis or primary non-function after transplant

• Calculated MELD score

• Exception MELD score
  • HCC, HPS, PPHtn, PSC with cholangitis, metabolic diseases, familial amyloid polyneuropathy (FAP)

• Inactive status

Waiting Lists

• Four lists based on blood type (O, A, B, AB)
  • Frequency based on ethnicity but generally O>A>B>AB
  • Creates inequality amongst blood types
  • Median MELD at transplant can vary amongst blood types (high 30s for blood type O and low 20s for blood type AB in our region)

• Blood type O can be allocated to other blood types in certain circumstances (status 1a, etc)

Simplified Adult Liver Allocation

1. Adult and pediatric status 1A within region
2. MELD 40 to 15 within the organ procurement organization’s (OPO) donation service area (DSA) and than within region
3. Adult or pediatric status 1A nationally
4. MELD <15 within DSA/region

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Regions

• 11 total regions in US
• California along with Arizona, Nevada, New Mexico, and Utah is in region 5
• Region 5 is a "high MELD" region
• Each region divided into donation service area (DSA) – USC is in same area as UCLA, Cedar Sinai, Loma Linda, and St. Vincent

https://optn.transplant.hrsa.gov/members/regions/
OPTN Regions

https://optn.transplant.hrsa.gov/members/regions/
Liver Transplantation at USC
Median Listed MELD scores for adult deceased donor liver transplant recipients in 2016

Percent of adults who underwent DDLT within 5 years of listing

Pre-transplant mortality rates among adults waitlisted for liver transplant in 2015-2016

How can we optimize the chance of the patient receiving a transplant?

• Overall organ shortage
  • 7841 transplant among 13726 patients on the waiting list in 2016
  • Use expanded criteria donors – older with comorbidities
  • HCV positive donors – on the rise given opioid epidemic
• Listing in other regions
  • Not possible for most given financial and insurance restraints
  • <1% of patients are listed in multiple regions
• Ultimately, we need changes to the allocation system and redistricting to optimize organ availability to all

https://unos.org/data/transplant-trends/
Live Donor Liver Transplant

• Healthy donors can donate up to 70% of their liver volume
• LDLT has excellent outcomes
  • Overall one-year graft survival of 90%
  • Decreased mortality when compared to deceased donor transplants when compared from time of listing (1-year survival 90% vs. 80%; p<0.001)
  • Higher rates of biliary complications (30%) but this decreases with center experience
• 401 living donor LT in 2018 in US
• USC performed 11 thus far in 2019

Summary

• Liver transplant is a potential life-saving procedure for some patients suffering from consequences of acute and chronic disease

• Patient selection starts by assessing for those who will have symptomatic or survival benefit from liver transplant

• A thorough pre-transplant assessment in a multi-disciplinary setting is key to appropriate patient selection

• Inherent flaws exist in the liver allocation system and certain measures may need to be taken to optimize patient’s chances of receiving a liver transplant (ie live donor liver transplant)
References

References