Indications for Liver Transplantation

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UCSF
Overview

• Liver 101
  – Function
• Cirrhosis of the Liver
  – Mechanisms of disease
  – Causes
  – Complications
• Indications for transplant
• Contraindications to transplant
• Organ allocation
• Special circumstances - MELD exceptions
Overview

• Acute Liver Failure
  – Definitions
  – Causes
• Management
• Role of Transplantation
  – Determining prognosis
  – Outcomes
The Liver - What it Does

- Detoxification
- Synthesis
- Blood clotting factors
- Plasma proteins

- Digestion
- Storage
- Metabolic & nutritional control
- Immunity
Cirrhosis of the Liver & End-Stage Liver Disease
Pathophysiology of Liver Disease
The Fundamentals

Inciting Agents → Organ Injury → Death

Organ Injury → Regeneration Repair

Regeneration Repair → Scar formation

Scar formation → Chronic disease/ Cirrhosis

Recovery

Repeated or Chronic Injury
Living Donor Transplantation
Made Possible by Regeneration

Right Lobe Graft

Left Lobe Graft

Photos courtesy of Robert S. Brown, Jr. MD, MPH; Columbia-Presbyterian Medical Center, New York.
Chronic toxic insult
Chronic viral hepatitis
Autoimmune disease
Fatty liver disease

Tissue destruction
Inflammation
Scarring
Regeneration

Normal
Cirrhosis
Histology

Stage 1

Stage 2

Stage 3

Stage 4
Causes of Cirrhosis

- Chronic Viral Hepatitis
  - Hepatitis C
  - Hepatitis B
- Alcohol
- Nonalcoholic steatohepatitis
- Cryptogenic
- Autoimmune diseases
  - Primary biliary cirrhosis (PBC)
  - Primary sclerosing cholangitis (PSC)
  - Autoimmune hepatitis
- Metabolic/metal storage diseases
  - Hemochromatosis
  - Wilson Disease
  - Alph-1-antitrypsin deficiency
- Pediatric liver diseases
  - Biliary atresia
  - Inborn error of metabolism
Jaundice  
Bruising  
Ascites  
Muscle wasting  
Varices  
Encephalopathy
Portal Hypertension: Varices

“Hypersplenism”
- Cytopenias
Risk of Bleeding:
- Large size
- Liver failure
  (Child Class C cirrhosis)
Progression of Ascites to Renal Failure

<table>
<thead>
<tr>
<th>Subtle sodium retention</th>
<th>Obvious sodium retention</th>
<th>Avid sodium retention</th>
<th>Functional renal failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-ascites</td>
<td>Responsive ascites</td>
<td>Refractory ascites</td>
<td>Hepatorenal syndrome</td>
</tr>
<tr>
<td>↑ ANF, ↓ PRA Normal or ↑ PNE</td>
<td>↑↑ ANF, normal or ↑ PRA, ↑ PNE</td>
<td>↑↑↑ ANF, ↑↑ PRA, ↑ PNE</td>
<td>ANF nonresponsiveness ↑↑↑ PRA, ↑↑↑ PNE</td>
</tr>
</tbody>
</table>
# Hepatic Encephalopathy

## West Haven Classification

<table>
<thead>
<tr>
<th>Stage</th>
<th>Consciousness</th>
<th>Personality &amp; Intellect</th>
<th>Neuro-motor</th>
<th>Ammonia level</th>
<th>EEG Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>Sub-Clinical (MHE)</td>
<td>Normal</td>
<td>Impaired psychomotor testing</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Grade 1</td>
<td>Insomnia, disturbed sleep pattern</td>
<td>Confusion, forgetfulness, agitation</td>
<td>Tremor, constructional apraxia, incoordination</td>
<td>↑</td>
<td>Slightly abnormal</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Lethargy</td>
<td>Disorientation, bizarre behavior</td>
<td>Asterixis, ataxia</td>
<td>↑↑</td>
<td>Slowing of triphasic waves</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Somnolence, but patient may be arousable</td>
<td>Disorientation, aggression</td>
<td>Asterixis, hyperactive reflexes, positive Babinski’s reflex</td>
<td>↑↑↑</td>
<td>Slowing of triphasic waves</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Coma, unresponsive</td>
<td>Coma</td>
<td>Decerebrate posture</td>
<td>↑↑↑↑</td>
<td>Slow waves (2 to 3 cycles per second)</td>
</tr>
</tbody>
</table>

Indications for Liver Transplantation

- Fulminant liver failure
- Complications of cirrhosis (variceal bleeding, hepatic encephalopathy, ascites, hepatorenal syndrome)
- Hepatocellular carcinoma
- Pulmonary syndromes
  - Hepatopulmonary syndrome
  - Portopulmonary hypertension
- Polycystic liver disease
- Metabolic diseases (Liver-based causing systemic disease)
  - Familial amyloidosis
  - Primary oxaluria
  - Glycogen storage disease
  - Urea cycle enzyme deficiencies
  - Tyrosinemia
  - MSUD
Contraindications and Controversies in Patient Selection

Absolute Contraindications

- Extrahepatic malignancy
- Liver cancer with macrovascular invasion
- Untreated AIDS
- Severe, uncontrolled systemic infection
- Multiorgan failure
- Advanced cardiopulmonary disease
- Irreversible, advanced brain damage
- Active substance abuse
- Lack of psychosocial support
- Technical/anatomical barriers
Contraindications and Controversies in Patient Selection

“Relative” Contraindications

- HIV seropositivity/AIDS on HAART
- Methadone maintenance
- Stage 3+ hepatocellular carcinoma
- Cholangiocarcinoma
- Re-transplantation for end-stage recurrent HCV
- Morbid obesity
- Advanced age
- Severe physical deconditioning
Liver Transplantation
Major Differences From Kidney Transplantation

- No artificial organ support
- Critical timing of transplantation
- High-risk living donor procedure
- Regenerative organ
- Recurrent diseases
- Simple donor matching (ABO, size)
- Less immunosuppression
  - “Immunologically privileged organ”
Liver Transplant Milestones

- 1963 - First human liver transplant by Thomas Starzl
- 1980’s - Introduction of CySA
- 1983 - National Institutes of Health Consensus Development Conference: liver transplantation is effective treatment
- 1990’s - Refinement in surgical technique, more potent and safer immunosuppressive drug regimens, improved comprehensive care; prevention of hepatitis B recurrence
- 1995 - Adult-to-adult living donor transplant in the USA
- 1998 - Curative transplantation for liver cancer
- 2002 - MELD system of liver allocation
- Current 1-year patient survival rates of 85 - 95%
Liver Transplants in the US
Deceased Donor Transplants
2007 – 2009
U.S.

# of Transplants

<table>
<thead>
<tr>
<th>Year</th>
<th>HL</th>
<th>HR</th>
<th>IN</th>
<th>KI</th>
<th>KP</th>
<th>LI</th>
<th>LU</th>
<th>PA</th>
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<tr>
<td>2007</td>
<td>29</td>
<td>2212</td>
<td>178</td>
<td>10441</td>
<td>854</td>
<td>6101</td>
<td>1659</td>
<td>379</td>
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</tbody>
</table>

2007 2008 2009
Liver Transplants by Etiology of Liver Disease
UNOS OPTN Data 1992-2007

Figure 1. Proportion of liver transplants for specific etiologies, 1992–2007.

O’Leary JG et al., Gastroenterology, 2008
Liver Transplants by Etiology of Liver Disease
UNOS OPTN Data 1/90-8/08

Annual Total (Range) 03-07
5673-6493
Liver Transplants by Etiology of Liver Disease
UNOS OPTN Data 1992-2006

Figure 2. Number of transplants for cryptogenic cirrhosis, HCC, and chronic hepatitis C by year.

O’Leary JG et al., Gastroenterology, 2008
Organ Allocation for Liver Transplantation
## Child-Turcotte-Pugh Classification

<table>
<thead>
<tr>
<th></th>
<th>1 point</th>
<th>2 points</th>
<th>3 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (g/dl)</td>
<td>&gt;3.5</td>
<td>2.8-3.5</td>
<td>&lt;2.8</td>
</tr>
<tr>
<td>Bilirubin (mg/dl)</td>
<td>&lt;2</td>
<td>2-3</td>
<td>&gt;3</td>
</tr>
<tr>
<td>INR</td>
<td>&lt;1.7</td>
<td>1.7-2.3</td>
<td>&gt;2.3</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
<td>Slight</td>
<td>Moderate</td>
</tr>
<tr>
<td>Encephalopathy (stage)</td>
<td>0</td>
<td>1-2</td>
<td>3-4</td>
</tr>
</tbody>
</table>

**CTP Class:** A: 5-6, B: 7-9; C: 10 or more.  MLC = 7
# Fundamental Change in Rules for Liver Allocation

**UNOS MELD/PELD Rules - 2/27/02**

## OLD UNOS RULES
- Status 1 - Fulminant liver failure
- Status 2A - ESLD in the ICU
- Status 2B - CTP C’s & HCC
- Status 3 CTP B’s
- Waiting time

## NEW RULES - MELD/PELD
- Status 1A - Fulminant liver failure
- Status 1B - Severely ill pediatric patients (PELD/MELD > 25, ICU)
- ESLD ranked by severity score (6-40)
  - MELD (Adults)
  - PELD (Children < 12)
- Exceptions
  - HCC
  - Other
- Status 7 - Temporarily unsuitable for transplant
Model for End-stage Liver Disease

- Based on simple, objective laboratory variables (plus age & physical data for PELD)
- MELD for age 12 and up; PELD for <12
- Variables identified through multivariate analysis in a population with ESLD
- Validated prospectively in an independent population with ESLD
- Reflects the risk or probability of death within 3 months if the patient does not receive a transplant
Model for End-stage Liver Disease

- MELD Risk Score = 10 x [0.957 x log e (creatinine mg/dL) + 0.378 x log e (bilirubin mg/dL) + 1.120 x log e (INR)] + 6.43

- Minimum values for creatinine, bilirubin and INR = 1.0. Creatinine maximum value = 4.0 (actual or default on dialysis)

- Score rounded to the nearest integer (range of 6 - 40)
Pediatric End-stage Liver Disease Score

- PELD Risk Score = \( 10 \times [-0.687 \times \log e (\text{albumin g/dL}) + 0.480 \times \log e (\text{bilirubin mg/dL}) + 1.857 \times \log e (\text{INR}) + 0.436 \text{ (if <1 year old)} + 0.667 \text{ (if growth failure present < -2 Standard deviations)}] \)

- Minimum values for albumin, bilirubin and INR = 1.0.

- Score rounded to the nearest integer (range of 6 - 40)
MELD/PELD

• Advantages
  – Objective
  – Works reasonably well to represent expected 3-month mortality

• Disadvantages
  – Under-represents risk in some patients
    • Hepatic encephalopathy; refractory ascites
  – Does not represent impact of disease on quality of life
  – Can be affected by “unrelated” interventions or disease
  – Inter-OPO & Inter-regional disparity
Geographic Prioritization in Liver Allocation

- Status 1A and 1B
  - Local, Regional, National
- MELD => 15
  - Local, Regional
Mean MELD ABO=O
24

Mean MELD ABO=O
30

Mean MELD ABO=O
22
MELD Exceptions
Indications for Liver Transplantation

- Fulminant liver failure (acute liver failure + altered mental status) **Status 1A**
- Complications of cirrhosis (variceal bleeding, hepatic encephalopathy, ascites, hepatorenal syndrome) **MELD**
- Hepatocellular carcinoma
- Pulmonary syndromes
  - Hepatopulmonary syndrome
  - Portopulmonary hypertension
- Polycystic liver disease
- Metabolic diseases (**Liver-based causing systemic disease**)  
  - Familial amyloidosis
  - Primary oxaluria
  - Glycogen storage disease
  - Urea cycle enzyme deficiencies
  - Tyrosinemia
  - MSUD
Liver Transplantation for HCC

- Selection - Stage 2 (T2) limit
- Survival rates at four years: 85% overall (of whom 92% recurrence-free) (Mazzaferro 1996)
- Overall 5 year survival: 70-75% with recurrence rates <15% (Llovet 1999, Yao 2001)
- Liver transplantation is overall the best treatment for early HCC if patients can make it to transplant
Liver Transplant for HCC
Milan Criteria (Stage II; T2)

Single, 2-5 cm

Up to 3, none > 3 cm

+ Absence of Macroscopic Vascular Invasion

+ Absence of Extrahepatic Spread

Mazzaferro et al., 1996
Improving Access to Liver Transplantation for HCC

UNOS Stage Criteria

- Expanded Donor Pool
- MELD Priority
- Living Donor

Expanded Criteria
“Downstaging” Therapies
Bridging Therapies

Time on Waiting List
Management of HCC

HCC - Increasing Allocation
MELD Priority

OLD UNOS RULES
- Status 1A - Fulminant live failure
- Status 2A - ESLD in the ICU
- Status 2B - CTP C’s & HCC
- Status 3 CTP B’s
- Waiting time

2002 RULES
- T1 = 24 points
- T2 = 29 points
- Points increase every 3 months waiting

2005 RULES
- T2 = 22 points
- Points increase every 3 months waiting (eq. to a 10% increase in mortality)
MELD Exception Score

Other Conditions That Qualify

• Polycystic liver disease
  – Evidence of nutritional failure
• Familial amyloidosis
  – Biopsy & TTR gene mutation confirmed, adequate performance status
• Glycogen storage disease
  – Adenomas
• Hepatopulmonary Syndrome
  – PO2 <60
• Portopulmonary hypertension
  – Presence of elevated MPAP [in absence of volume overload] and PVR responsive to medical therapy
• Primary hyperoxaluria
  – On HD with liver biopsy-proven AGT enzyme deficiency
• Cholangiocarcinoma
  – Protocol in place
Acute Liver Failure
Acute Liver Injury

Acute Liver Failure (ALF)*

- Non-Fulminant
- Fulminant

Mild

Elevated ALT/AST

+ Coagulopathy (INR>2.0)

+ Hepatic encephalopathy

*~2000 cases per year in the US
Loss of Critical Liver Homeostatic Functions

- Protein synthesis - Coagulopathy (INR!!!)
- Excretion - Bilirubin (Jaundice)
- Detoxification - Urea Cycle (Ammonia - Encephalopathy, Brain Edema)
- Acid base balance - Acidosis
- Renal homeostasis - Renal failure
- Immune (Kupfer cell) function - Infection
Fulminant Liver Failure

- Acute liver injury plus altered mental state 2° to hepatic encephalopathy (HE)
- Onset of HE:
  - Within 26 weeks of jaundice (General)
  - Within 8 weeks of initial symptoms (UNOS)
- Severe coagulopathy
- No evidence of pre-existing chronic liver disease*

* Exceptions
  - Wilson’s Disease
  - AIH
ALFSG Outcomes

1321 FHF subjects enrolled
549 (42%) listed

Spontaneous survivors
47%

Transplanted
25%

Died - Not Transplanted
28%

Alive at 3 wks
89%

Overall survival:
\( n = 912 \) (69%)
Etiology of ALF in the US

- Acetaminophen: 46%
- Drug: 15%
- Viral: 15%
- Autoimmune: 15%
- Indeterminate: 15%

- Acetaminophen
- Drug
- Hepatitis B
- Hepatitis A
- Autoimmune
- Ischemic
- Wilson
- Budd-Chiari
- Pregnancy
- Other
- Indeterminate
## Medications Containing Acetaminophen

<table>
<thead>
<tr>
<th>OTC</th>
<th>Prescription</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tylenol</td>
<td>Darvocet</td>
</tr>
<tr>
<td>Dayquil</td>
<td>Fioricet</td>
</tr>
<tr>
<td>Theraflu</td>
<td>Lorcet</td>
</tr>
<tr>
<td>Feverall</td>
<td>Lortab</td>
</tr>
<tr>
<td>Legatrin</td>
<td>Midrin</td>
</tr>
<tr>
<td>Nyquil</td>
<td>Norco</td>
</tr>
<tr>
<td>Excedrin</td>
<td>Norel Plus</td>
</tr>
<tr>
<td>Pamprin</td>
<td>Percocet</td>
</tr>
<tr>
<td></td>
<td>Tylenol with Codeine</td>
</tr>
<tr>
<td></td>
<td>Ultracet</td>
</tr>
<tr>
<td></td>
<td>Vicodin</td>
</tr>
</tbody>
</table>
Cytochrome p450 2E1 (phase I)

\[
\begin{align*}
\text{HN} & \quad \text{CH}_3 \\
\text{O} & \\
\text{N} & \\
\text{O} & \\
\text{H} & \\
\text{HO} &
\end{align*}
\]

Cytochrome p450 2E1 (phase I)