End Stage Liver Disease &
Disease Specific Indications for Liver Transplant

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Introduction...

Transplants By Organ Type - 2017
Based on OPTN data as of June 28, 2018

<table>
<thead>
<tr>
<th>Organ</th>
<th>Transplants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>19,850</td>
</tr>
<tr>
<td>Liver</td>
<td>8,082</td>
</tr>
<tr>
<td>Pancreas</td>
<td>213</td>
</tr>
<tr>
<td>Kidney / Pancreas</td>
<td>789</td>
</tr>
<tr>
<td>Heart</td>
<td>3,244</td>
</tr>
<tr>
<td>Lung</td>
<td>2,449</td>
</tr>
<tr>
<td>Heart / Lung</td>
<td>29</td>
</tr>
<tr>
<td>Intestine</td>
<td>109</td>
</tr>
<tr>
<td>Head &amp; Neck: Craniofacial</td>
<td>1</td>
</tr>
<tr>
<td>GU: Uterus</td>
<td>4</td>
</tr>
<tr>
<td>Upper Limb: Bilateral</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>34,771</strong></td>
</tr>
</tbody>
</table>
The Gift of Life
Lovingly placed by their family and friends, each medallion in this fountain commemorates an individual who gave the gift of life and health to others through organ, eye and tissue donation.
What does the liver do?

- STORAGE
- METABOLIC
- DETOXIFICATION
- SYNTHETIC FUNCTIONS
- EXCRETORY FUNCTIONS (bile)
- ...AND MORE!!!!
What is liver cirrhosis?

- End result of the fibrogenesis that occurs with chronic liver injury

- Compensated vs. Decompensated
Indicators for liver failure

- Liver decompensation
  - Sequelae of portal hypertension
  - Synthetic dysfunction

- Considerations re: quality of life
Natural History of Liver Cirrhosis

Manifestations of Decompensation

- Ascites + edema
- Variceal bleeding
- Encephalopathy
- Jaundice
- Multiple complications

(Adapted from Fattovich G et al. Gastroenterology. 1997;112:466)
Disease processes leading to the need for liver transplantation
Objectives

- Discuss brief disease process overview: hepatitis B, hepatitis C, fatty liver/NASH, and HCC
- Discuss current liver transplant trends with respect to these disease processes
Hepatitis B
Hepatitis B

- ~240 million with chronic hepatitis B (CHB)
  - Predominantly in Africa & Asia

- Possibly as high as 2.2 million in United States (US)
  - 1991 routine vaccination recommended
  - 2014: slight increase r/t IVDA

- Global deaths
  - Cirrhosis: 310K
  - HCC: 340K

(https://www.cdc.gov/hepatitis/hbv/hbvfaq.htm#overview)
Hepatitis B

What is it?
- Liver infection caused by the hepatitis B virus (HBV)
  - DNA virus, not yet curable
  - Transmission: vertical, blood/body fluids
- Can be acute or chronic
  - Acute (new infection)
    - Can sometimes self-resolve
    - Can cause acute liver failure requiring liver transplant (LT)
    - Asymptomatic or asymptomatic
  - Chronic
    - Usually vertically transmitted
    - Risk for developing hepatocellular carcinoma (HCC), and liver cirrhosis
      - Can develop HCC even without underlying cirrhosis
    - Asymptomatic or symptomatic

https://www.cdc.gov/hepatitis/hbv/hbvfaq.htm#overview)
Hepatitis B

- Symptoms
  - Fever, fatigue, loss of appetite, nausea, vomiting, abdominal pain, jaundice (dark urine, clay colored stools), joint pain

- Can it be prevented?
  - Vaccination
  - Avoiding risks for exposure

(https://www.cdc.gov/hepatitis/hbv/hbvfaq.htm#overview)
Hepatitis B

How is it diagnosed?

Screening blood tests (CDC recs)

- Hepatitis B surface antigen (HBsAg) → Indicates current infection
  - Considered chronic if HBsAg persists > 6 months
- Hepatitis B surface antibody (HBsAb) → Indicates immunity via vaccination, or prior exposure + spontaneous clearance and acquired immunity
- Hepatitis B core antibody IgG (HBcAb IgG/total) → indicates prior exposure
  - Can be positive in current infection, use in conjunction with other tests
TABLE 3. Groups at High Risk for HBV Infection Who Should Be Screened

- Persons born in regions of high or intermediate HBV endemicity (HBsAg prevalence of ≥2%)
  - Africa (all countries)
  - North, Southeast, East Asia (all countries)
  - Australia and South Pacific (all countries except Australia and New Zealand)
  - Middle East (all countries except Cyprus and Israel)
  - Eastern Europe (all countries except Hungary)
  - Western Europe (Mallorca, Spain, and indigenous populations of Greenland)
  - North America (Alaskan natives and indigenous populations of Northern Canada)
  - Mexico and Central America (Guatemala and Honduras)
  - South America (Ecuador, Guyana, Suriname, Venezuela, and Amazonian areas)
  - Caribbean (Antigua-Barbuda, Dominica, Grenada, Haiti, Jamaica, Saint Kitts and Nevis, Saint Lucia, and Turks and Caicos Islands)
- U.S.-born persons not vaccinated as an infant whose parents were born in regions with high HBV endemicity (≥8%)*
- Persons who have ever injected drugs*
- Men who have sex with men*
- Persons needing immunosuppressive therapy, including chemotherapy, immunosuppression related to organ transplantation, and immunosuppression for rheumatological or gastroenterologic disorders.
- Individuals with elevated ALT or AST of unknown etiology*
- Donors of blood, plasma, organs, tissues, or semen
- Persons with end-stage renal disease, including predialysis, hemodialysis, peritoneal dialysis, and home dialysis patients*
- All pregnant women
- Infants born to HBsAg-positive mothers*
- Persons with chronic liver disease, e.g., HCV*
- Persons with HIV*
- Household, needle-sharing, and sexual contacts of HBsAg-positive persons*
- Persons who are not in a long-term, mutually monogamous relationship (e.g., >1 sex partner during the previous 6 months)*
- Persons seeking evaluation or treatment for a sexually transmitted disease*
- Healthcare and public safety workers at risk for occupational exposure to blood or blood-contaminated body fluids*
- Residents and staff of facilities for developmentally disabled persons*
- Travelers to countries with intermediate or high prevalence of HBV infection*
- Persons who are the source of blood or body fluid exposures that might require postexposure prophylaxis
- Inmates of correctional facilities*
- Unvaccinated persons with diabetes who are aged 19 through 59 years (discretion of clinician for unvaccinated adults with diabetes who are aged ≥60 years)*

*Indicates those who should receive hepatitis B vaccine, if seronegative.

(Terrault et al., 2018)
Hepatitis B serologies

- **HBsAg**: if positive, indicates current infection
- **HBsAb**: if positive, indicates immunity (vaccinated, or naturally acquired)
- **HBcAb**: if positive, indicates prior HBV exposure
  - IgM: seen in acute HBV
  - IgG
- **HBeAg**: if positive, indicates high replication
- **HBeAb**: if positive, indicates low replication
- **HBV DNA**: amount of virus in the blood/mL
## Hepatitis B serologies - crash course!

### Interpretation of Hepatitis B Serology Test Results

<table>
<thead>
<tr>
<th>HBsAg</th>
<th>HBV DNA</th>
<th>HBcAb (IgM)</th>
<th>HBcAb (IgG)</th>
<th>HbeAg</th>
<th>HBeAb</th>
<th>HBsAb</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Susceptible to HBV infection</td>
</tr>
<tr>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>-</td>
<td>-</td>
<td>Acute HBV</td>
</tr>
<tr>
<td>✓</td>
<td>✓</td>
<td>-</td>
<td>✓</td>
<td>+/-</td>
<td>+/-</td>
<td>-</td>
<td>Chronic HBV (&gt; 6 months)</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>✓</td>
<td>-</td>
<td>-</td>
<td>✓</td>
<td>Immune to HBV (past infection)</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>✓</td>
<td>Immune to HBV (vaccinated)</td>
</tr>
</tbody>
</table>

**Figure 6 - Interpretation Hepatitis B Serology Testing Results**

Clinical stages of HBV

- **HBeAg+**
  - Normal ALT
  - DNA ++++
- **HBeAg+**
  - Elevated ALT
  - DNA +++
- **HBeAg+**
  - Elevated ALT
  - DNA ++
  - Albumin
  - Platelets
- **HBeAg-**
  - Normal ALT
  - DNA + / -
- **HBeAg-**
  - Elevated ALT
  - DNA ++
  - Albumin
  - Platelets

ALT: Alanine Aminotransferase
HBV DNA: Hepatitis B Viral DNA

(Tong et al, 2011)
Treatment of hepatitis B

- Treatment initiated for “active” HBV (varying guidelines/treatment recommendations exist)
  - High ALT + High HBV DNA
  - Once daily oral pill, long term therapy
    - No cure, but good viral suppression
    - Well tolerated, minimal SE’s

- Other indicators for antiviral therapy
  - Strong family history of HCC
  - Patient history of HCC
  - Underlying liver cirrhosis
  - Immunosuppressive therapy
Hepatitis B monitoring and HCC surveillance

- Laboratory tests every 6-12 months
  - Monitor AFP (tumor marker), liver tests, and HBV DNA levels

- Abdominal ultrasounds every 6-12 months
  - Dependent on HBV stage + risk factors
  - If cirrhosis, always q6 months
  - Contrast enhanced MRI/CT as clinically indicated

- Those who already have a history of HCC/HCC treatment
  - Usually contrast enhanced scan (MRI, CT), can be as often as every 3 months

- Ongoing liver transplant needs assessment
Hepatitis C
Hepatitis C

- Symptoms
  - Similar to HBV

- Can it be prevented?
  - Avoiding risks for exposure
  - No vaccine available
What is Hepatitis C?

**What is it?**
- Liver infection caused by the hepatitis C (HCV) virus
  - RNA virus, now CURABLE!!!
  - Usually through parenteral exposures to blood/body fluid containing blood
    - Prevalent in the “Baby Boomer” population
  - Can be vertically transmitted, not as common as HBV

**Can be acute or chronic**
- Acute (new infection)
  - Can sometimes self resolve
  - Not typically known to cause acute liver failure requiring LT like acute HBV
  - Asymptomatic or symptomatic
- Chronic
  - Risk for progression to liver cirrhosis and development of HCC
    - Unlike HBV, usually only develop HCC in setting of cirrhosis
    - Asymptomatic or symptomatic

(https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm#section1)
Hepatitis C

How is it diagnosed?

- Screening blood test
  - Hepatitis C antibody (HCV Ab)
    - If positive: current or past infection
    - Does NOT indicate immunity!

- Confirmatory test
  - Hepatitis C RNA quantitation
    - Considered to be chronic if HCV RNA persists for > 6 months

- Genotype (GT) test
  - Seven distinct genotypes identified
    - GT 1 most common in US
    - Can be used to determine treatment course
  - > 67 subtypes identified
Who is at risk for HCV?

- IVDA users (most common in US)
- Recipients of clotting factor concentrates made before 1987
- Blood transfusions/solid organ transplant recipients before 1992
- Chronic HD patients
- Known HCV exposures (healthcare workers, HCV positive blood/organ donors)
- HIV infected
- Children born to HCV positive mothers
- “Baby Boomers”
Recommended Testing Sequence for Identifying Current Hepatitis C Virus (HCV) Infection

For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody is recommended. For persons who are immunocompromised, testing for HCV RNA can be considered.

To differentiate past, resolved HCV infection from biologic false positivity for HCV antibody, testing with another HCV antibody assay can be considered. Repeat HCV RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.

FDA-approved direct-acting antivirals for hepatitis C

2013
- Brand name: OLYSIO
  - Generic name: Simeprevir
  - Genotype: 1
  - Company: Janssen

- Brand name: SOVALDI
  - Generic name: Sofosbuvir
  - Genotype: 1, 2, 3 or 4
  - Company: Gilead Sciences

2014
- Brand name: HARVONI
  - Generic name: Ledipasvir/sofosbuvir
  - Genotype: 1
  - Company: Gilead Sciences

2015
- Brand name: TECHNIVIE
  - Generic name: Ombitasvir/paritaprevir/ritonavir
  - Genotype: 4
  - Company: AbbVie

2016
- Brand name: ZEPATIER
  - Generic name: Elbasvir/Grazoprevir
  - Genotype: 1 or 4
  - Company: Merck

- Brand name: EPCLUSA
  - Generic name: Sofosbuvir/Velpatasvir
  - Genotype: 1, 2, 3, 4, 5 or 6
  - Company: Gilead Sciences

2017
- Brand name: VOSEVI
  - Generic name: Sofosbuvir/Velpatasvir/Voxilaprevir
  - Genotype: 1, 2, 3, 4, 5 or 6
  - Company: Gilead Sciences

Brand name: VIEKIRA PAK
- Generic name: Dasabuvir/Ombitasvir/Paritaprevir/Ritonavir
- Genotype: 1
- Company: AbbVie

Brand name: DAKLINZA
- Generic name: Daclatasvir
- Genotype: 3
- Company: Bristol-Myers Squibb
Hepatitis C (misc.)

- All HCV patients should be screened for HBV infection
- All HCV patients with cirrhosis need to be screened for HCC with at least an abdominal ultrasound q6 months
- Ongoing assessment for need for LT
- CURABLE disease
  - Oral therapy, typically 8-12 weeks
    - Medication usually dictated by insurance coverage
  - Well tolerated, with minimal SE’s
  - Once cured, CAN be re-infected with re-exposure!!!
Non-alcoholic fatty liver disease (NAFLD) & non-alcoholic steatohepatitis (NASH)
NAFLD

Definition

- Evidence of hepatic steatosis (imaging or histology) and lack of secondary causes of fat accumulation (alcohol, steatogenic medication, monogenic hereditary disorders)

- Associated with metabolic comorbidities
  - Obesity
  - Diabetes
  - Dyslipidemia

(Chalasani et al., 2017)
NAFL vs. NASH

+ **NAFL**
  - Presence of $\geq 5\%$ hepatic steatosis without evidence of hepatocellular injury in the form of hepatocyte ballooning

+ **NASH**
  - Presence of $\geq 5\%$ hepatic steatosis and inflammation with hepatocyte injury (ballooning), with or without any fibrosis
  - Though rare, can develop HCC even in the absence of cirrhosis

(Chalasani et al., 2017)
NASH

Slide of histology of NASH
**TABLE 3. Risk Factors Associated With NAFLD**

<table>
<thead>
<tr>
<th>Common Conditions With Established Association</th>
<th>Other Conditions Associated With NAFLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>T2DM</td>
<td>Obstructive sleep apnea</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Hypopituitarism</td>
</tr>
<tr>
<td>MetS*</td>
<td>Hypogonadism</td>
</tr>
<tr>
<td>Polycystic ovary syndrome</td>
<td>Pancreatoduodenal resection</td>
</tr>
<tr>
<td></td>
<td>Psoriasis</td>
</tr>
</tbody>
</table>

*The Adult Treatment Panel III clinical definition of MetS requires the presence of three or more of the following features: (1) waist circumference greater than 102 cm in men or greater than 88 cm in women; (2) TG level 150 mg/dL or greater; (3) HDL cholesterol level less than 40 mg/dL in men and less than 50 mg/dL in women; (4) systolic blood pressure 130 mm Hg or greater or diastolic pressure 85 mm Hg or greater; and (5) fasting plasma glucose level 110 mg/dL or greater.*

(Chalasani et al., 2017)
Fatty liver

Treatment

- Treating/optimizing underlying metabolic conditions
- Lifestyle modification, including weight loss
  - Can consider bariatric surgery
- Medical therapies specifically for fatty liver/NASH still being studied, no “miracle cure”
- LT for those who progress to decompensated liver cirrhosis

- On trajectory to become leading cause for LT in the US
Disease-Specific Indications for OLT

**Hepatocellular Carcinoma**
- ALL cirrhotics and patients with chronic HBV are at risk for developing HCC
- Treatment
  - Resection
  - Locoregional therapies
  - Liver transplant
    - Exception points
  - Systemic therapies for advanced disease
Now...what about current disease trends for these diseases???
Figure LI 5. Distribution of adults waiting for liver transplant by diagnosis. Candidates waiting for transplant at any time in the given year. Candidates listed concurrently at multiple centers are counted once. Active and inactive patients are included. HCV, hepatitis C virus; ALD, alcoholic liver disease; Chol. disease, cholestatic disease.
Figure LI 27. Rates of livers recovered for transplant and not transplanted by HCV status. Percentages of livers not transplanted out of all livers recovered for transplant. HCV, hepatitis C virus.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>2006</th>
<th></th>
<th>2016</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Percent</td>
<td>N</td>
<td>Percent</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute liver failure</td>
<td>551</td>
<td>3.5%</td>
<td>226</td>
<td>1.6%</td>
</tr>
<tr>
<td>HCV</td>
<td>4804</td>
<td>30.9%</td>
<td>3117</td>
<td>22.7%</td>
</tr>
<tr>
<td>Alcoholic liver disease</td>
<td>3633</td>
<td>23.4%</td>
<td>3712</td>
<td>27.0%</td>
</tr>
<tr>
<td>Cholestatic disease</td>
<td>1602</td>
<td>10.3%</td>
<td>1124</td>
<td>8.2%</td>
</tr>
<tr>
<td>HCC</td>
<td>295</td>
<td>1.9%</td>
<td>1130</td>
<td>8.2%</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>4641</td>
<td>29.9%</td>
<td>4417</td>
<td>32.2%</td>
</tr>
<tr>
<td>Blood type</td>
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<tr>
<td>A</td>
<td>5784</td>
<td>37.3%</td>
<td>5263</td>
<td>38.3%</td>
</tr>
<tr>
<td>B</td>
<td>1743</td>
<td>11.2%</td>
<td>1564</td>
<td>11.4%</td>
</tr>
<tr>
<td>AB</td>
<td>401</td>
<td>2.6%</td>
<td>355</td>
<td>2.6%</td>
</tr>
<tr>
<td>O</td>
<td>7598</td>
<td>48.9%</td>
<td>6544</td>
<td>47.7%</td>
</tr>
<tr>
<td>Medical urgency</td>
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</tr>
<tr>
<td>Status 1A</td>
<td>3</td>
<td>0.0%</td>
<td>1</td>
<td>0.0%</td>
</tr>
<tr>
<td>MELD ≥ 35</td>
<td>28</td>
<td>0.2%</td>
<td>51</td>
<td>0.4%</td>
</tr>
<tr>
<td>MELD 30-34</td>
<td>24</td>
<td>0.2%</td>
<td>383</td>
<td>2.8%</td>
</tr>
<tr>
<td>MELD 15-29</td>
<td>2939</td>
<td>18.9%</td>
<td>4356</td>
<td>31.7%</td>
</tr>
<tr>
<td>MELD &lt; 15</td>
<td>9025</td>
<td>58.1%</td>
<td>6349</td>
<td>46.3%</td>
</tr>
<tr>
<td>Unknown</td>
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<td>0.0%</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>Inactive</td>
<td>3506</td>
<td>22.6%</td>
<td>2586</td>
<td>18.8%</td>
</tr>
<tr>
<td>Exception status</td>
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</tr>
<tr>
<td>None</td>
<td>14,965</td>
<td>96.4%</td>
<td>11,082</td>
<td>80.7%</td>
</tr>
<tr>
<td>HCC</td>
<td>407</td>
<td>2.6%</td>
<td>1918</td>
<td>14.0%</td>
</tr>
<tr>
<td>Other</td>
<td>154</td>
<td>1.0%</td>
<td>726</td>
<td>5.3%</td>
</tr>
<tr>
<td>All candidates</td>
<td>15,526</td>
<td>100.0%</td>
<td>13,726</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Table LI 2 Clinical characteristics of adults on the liver transplant waiting list on December 31, 2006 and December 31, 2016. Candidates waiting for transplant on December 31, 2006, and December 31, 2016, regardless of first listing date; multiple listings are collapsed. HCC, hepatocellular carcinoma; HCV, hepatitis C virus.
Figure LI 7. Distribution of adults waiting for liver transplant by BMI. Candidates waiting for transplant at any time in the given year. Candidates listed concurrently at multiple centers are counted once. Active and inactive patients are included.
Figure LI 9. Deceased donor liver transplant rates among active adult waitlist candidates by sex and HCC exception status. Transplant rates are computed as the number of deceased donor transplants per 100 patient-years of active wait time in a given year. Individual listings are counted separately. Rates with less than 10 patient-years of exposure are not shown. Hepatocellular carcinoma (HCC) candidates have active Stage 2 exception points (per OPTN policy 9.3.G) in the given year.
Disease processes continued...