CIRRHOSIS AND LIVER CANCER MORTALITY

- Cirrhosis is a common cause of mortality in young adults.
  - 5\textsuperscript{th} most common cause of death for age 45-64 years.
  - 6\textsuperscript{th} most common cause of death for age 25-44 years.
- Mortality from liver disease is rising:
  - Chronic HCV epidemic
  - Fatty liver disease
  - Increased rates of liver cancer
LIVER TRANSPLANT
ACCESS TO CARE

• ~16,000 persons waiting for a liver transplant
• ~6,000 liver transplants are performed annually
• ~100 liver transplant programs
  ▪ The majority of patients with cirrhosis live more than 2 hours or 100 miles from a liver transplant center
  ▪ Travel to the transplant center for routine visits is costly, time consuming, associated with loss of work, income and is emotionally and physically demanding on the patient.

LIVER TRANSPLANT
PRE-TRANSPLANT MANAGEMENT

• Identify the patient with liver disease at increased risk for liver related mortality
• Manage complications of cirrhosis
• Screen for liver cancer
• Recognizing special circumstances which require liver transplantation sooner
  ▪ Pulmonary complications of cirrhosis
  ▪ Polycystic liver disease
• Evaluate for other diseases which would preclude a patient from LT
  ▪ COPD
  ▪ Cardiac disease
### ASSESSING MORTALITY
CHILD CLASS AND MELD SCORE

<table>
<thead>
<tr>
<th>MELD SCORE</th>
<th>CTP Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INR</strong></td>
<td>1 point</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>2 points</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>3 points</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th> </th>
<th> </th>
<th><strong>INR</strong></th>
<th> </th>
<th> </th>
</tr>
</thead>
<tbody>
<tr>
<td> </td>
<td> </td>
<td>1.7</td>
<td> </td>
<td>2.3</td>
</tr>
<tr>
<td> </td>
<td> </td>
<td>&gt;2.3</td>
<td> </td>
<td>3</td>
</tr>
<tr>
<td><strong>INR</strong></td>
<td><strong>&lt; 1.7</strong></td>
<td></td>
<td><strong>&lt; 2</strong></td>
<td></td>
</tr>
<tr>
<td><strong>&lt; 1.7</strong></td>
<td><strong>1.7-2.3</strong></td>
<td></td>
<td><strong>2-3</strong></td>
<td></td>
</tr>
<tr>
<td><strong>&gt; 2.3</strong></td>
<td><strong>&gt; 3</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>INR</strong></td>
<td><strong>&lt; 2</strong></td>
<td></td>
<td><strong>&lt; 3</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Total Bilirubin</strong></td>
<td><strong>&gt; 3.5</strong></td>
<td></td>
<td><strong>2.8-3.5</strong></td>
<td></td>
</tr>
<tr>
<td><strong>&gt; 3</strong></td>
<td><strong>&lt; 2.8</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Albumin</strong></td>
<td><strong>&gt; 3.5</strong></td>
<td></td>
<td><strong>2.8-3.5</strong></td>
<td></td>
</tr>
<tr>
<td><strong>&lt; 2.8</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ascites</strong></td>
<td>None</td>
<td></td>
<td>Mild</td>
<td>Mod-Severe</td>
</tr>
<tr>
<td><strong>None</strong></td>
<td><strong>Moderate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Severe</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HE</strong></td>
<td><strong>None</strong></td>
<td></td>
<td>Grade 1-2</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td><strong>Total Points</strong></td>
<td><strong>1 Yr Mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>20-29</strong></td>
<td><strong>20%</strong></td>
<td></td>
<td><strong>53%</strong></td>
<td><strong>Child class A</strong></td>
</tr>
<tr>
<td><strong>30-39</strong></td>
<td><strong>53%</strong></td>
<td></td>
<td><strong>71%</strong></td>
<td><strong>Child class B</strong></td>
</tr>
<tr>
<td><strong>40+</strong></td>
<td><strong>71%</strong></td>
<td></td>
<td><strong>10-15</strong></td>
<td><strong>Child class C</strong></td>
</tr>
<tr>
<td><strong>%</strong></td>
<td><strong>%</strong></td>
<td></td>
<td><strong>%</strong></td>
<td><strong>%</strong></td>
</tr>
<tr>
<td><strong>20%</strong></td>
<td><strong>29%</strong></td>
<td></td>
<td><strong>55%</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Total Points</strong></td>
<td><strong>1 Yr Mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- It is important to look at both the CTP and MELD scores.
- Complications of cirrhosis which do not factor into the MELD score calculation:
  - Ascites
  - HE
  - Esophageal or gastric varices
  - Serum albumin
  - Thrombocytopenia
  - All are risk factors for increased long term mortality from cirrhosis.
LIVER TRANSPLANT
WAITING TIME

• There is no such thing as a National waiting list
• 11 regions in USA
• Numerous OPOs within each region/state
• Function of the OPO
  ▪ Gain permission from family members for donation
  ▪ Transport organs to the matching transplant center
• Transplant MELD is based upon:
  ▪ Donation rate within the OPO
  ▪ Number of transplant centers within the OPO
  ▪ Number of patients waiting within the OPO

LIVER TRANSPLANT
UNOS REGIONS
LIVER TRANSPLANT
ALCOHOL

• Common cause for cirrhosis
• Less common indication for liver transplant
  ▪ Many patients do not stop consuming alcohol
  ▪ Poor social support systems
  ▪ Patients who abstain frequently get better
• Liver transplant programs have strict psycho-social criteria for patients with ETOH induced cirrhosis
  ▪ Mandatory 6 months of abstinence
  ▪ Mandatory counseling
  ▪ Random alcohol testing
  ▪ Delays the ability of the patient to be listed
  ▪ Reduces the likelihood for liver transplant

LIVER TRANSPLANT
HCC

• The incidence of HCC is rising
  ▪ Chronic HCV: Accounts for ~80% of HCC
  ▪ NAFLD: Can develop HCC in absence of cirrhosis
• Ultrasound all patients with cirrhosis Q 6 Months
• AFP is not necessary.
  ▪ 30% of HCC are AFP normal
  ▪ High AFPS are common without HCC
• Reserve CT and MRI for suspicious lesions on US
  ▪ Must be done as Triple phase study
  ▪ 90% accuracy
  ▪ Do not biopsy lesions that are characteristic of HCC
### HCC STAGING

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Priority for LT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Single lesion &lt; 2 cm</td>
<td>No</td>
</tr>
</tbody>
</table>
| 2     | 1 lesion 2-5 cm in diameter  
2-3 lesions 1-3 cm in diameter | Yes |
| 3     | 1 lesion > 5 cm in diameter  
>3 lesions 1-3 cm in diameter | No |
| 4     | Evidence of Vascular invasion  
Evidence of disease outside the liver | No |

### HCC APPROACH TO THE PATIENT

<table>
<thead>
<tr>
<th>Stage</th>
<th>Treatment options</th>
<th>HCV or HBV</th>
</tr>
</thead>
</table>
| 1     | Resection  
TACE  
Microwave or RFA  
Observe till stage 2 | Yes  
Yes  
Yes  
Yes |
| 2     | Resection  
TACE  
Liver transplant | Yes  
Yes  
Suppress to LT |
| 3     | Resection  
Downstage with radioembolization/TACE/etc  
Sorafenib | Yes  
Yes  
No  
No |
| 4     | Sorafenib | No |
LIVER TRANSPLANTATION PATIENTS ALIVE

Long term survival is dependent upon how well the adverse events which develop after liver transplantation are managed.

- Complications of immune suppressive medications
- Malignancy
- Recurrence of primary liver disease
- Biliary tract complications
- Infections
- General health issues
- Graft rejection
**IMMUNE SUPPRESSION AGENTS**

**MAJOR ADVERSE EFFECTS**

<table>
<thead>
<tr>
<th></th>
<th>Cyclosporine</th>
<th>Tacrolimus</th>
<th>Sirolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcineurin inhibitor</td>
<td>Calcineurin inhibitor</td>
<td>mTor receptor inhibitor</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>Hypertension</td>
<td>Hyperlipidemia</td>
<td></td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>Renal insufficiency</td>
<td>Delayed wound healing</td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>Diabetes mellitus</td>
<td>Cytopenia</td>
<td></td>
</tr>
<tr>
<td>Hirsuitism</td>
<td>Alopecia</td>
<td>Myopathy, Edema</td>
<td></td>
</tr>
<tr>
<td>Gout</td>
<td>Neurotoxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gingival hyperplasia</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**LIVER TRANSPLANTATION**

**HYPERTENSION**

- Calcineurin inhibitors
- Occurs in 70% of patients
- Etiology:
  - Afferent arteriolar vasoconstriction
  - Increase in renin, endothelin aldosterone
  - Sodium and water retention
- Treatment:
  - Calcium channel blockers
  - Alpha-blockers
  - Beta-blockers
  - ACE inhibitors
# LIVER TRANSPLANTATION

## RENAL INSUFFICIENCY

<table>
<thead>
<tr>
<th></th>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>&gt;50%</td>
<td>30% ESRD</td>
</tr>
<tr>
<td>Etiology</td>
<td>CNI inhibitor</td>
<td>CNI inhibitor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ischemia, fibrosis</td>
</tr>
<tr>
<td>Co-factors</td>
<td>Medications</td>
<td>Diabetes Mellitus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypertension</td>
</tr>
<tr>
<td>Treatment</td>
<td>Decrease CNI</td>
<td>D/C CNI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal transplant</td>
</tr>
</tbody>
</table>

---

## RENAL INSUFFICIENCY

### ACUTE AND CHRONIC

<table>
<thead>
<tr>
<th>Years</th>
<th>Serum Creatinine (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>4</td>
<td>1.5</td>
</tr>
<tr>
<td>6</td>
<td>2.0</td>
</tr>
<tr>
<td>8</td>
<td>2.5</td>
</tr>
<tr>
<td>10</td>
<td>3.0</td>
</tr>
<tr>
<td>12</td>
<td>3.5</td>
</tr>
<tr>
<td>14</td>
<td>4.0</td>
</tr>
</tbody>
</table>

- Prograf
- Switch to Sirolimus

---

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LIVER TRANSPLANTATION
MALIGNANCY

- Cutaneous
- Lymphoma
  - Monoclonal
  - Polyclonal (pseudolymphoma)
- Kaposi sarcoma
- Colon cancer
- Other cancer risks similar to that observed in general population

LIVER TRANSPLANTATION
CUTANEOUS MALIGNANCY

- Cell types
  - Squamous cell
  - Basal cell
- Nearly 6-fold more common than in general population
- Account for 50% of cancers in transplant recipients
- Sun exposure increases risk
- Risk increases with duration of immunosuppression
LIVER TRANSPLANTATION
LYMPHOPROLIFERATIVE DISORDERS

- 10-fold more common than in general population
- Monoclonal lymphoma:
  - Develops in 1-3% of transplant recipients
  - B-cell non-Hodgkins lymphoma
  - Develops within 1-3 years of transplant
  - Responds poorly to chemotherapy
- Polyclonal pseudolymphoma
  - Long term effect of immunosuppression
  - Reduce immune suppression
  - Treat co-existent EBV with acyclovir

LIVER TRANSPLANTATION
ULCERATIVE COLITIS

- Present in 70-90% of patients with sclerosing cholangitis
- Significantly increased risk of colon cancer
- Immunosuppression may decrease disease activity
- Reappearance of symptoms may be due to:
  - CMV colitis
  - C difficile
  - Other infectious agents
  - Acute worsening of colitis
COMPARED TO GENERAL POPULATION
COLON CANCER


LIVER TRANSPLANTATION
RECURRENCE OF DISEASE

- Hepatitis C virus
- Hepatitis B virus
- Hemochromatosis
- Non-alcoholic fatty liver disease
- Alcoholic fatty liver disease
- Primary biliary cirrhosis
- Sclerosing cholangitis
LIVER TRANSPLANTATION
HEPATITIS B

- Without treatment will recur in:
  - >90% of patients with chronic disease
  - < 10% of patients with acute HBV and fulminant hepatic failure
  - Virus in extrahepatic sites
  - Infects graft within days to weeks

- Prevention:
  - Hepatitis B immune globulin
  - Tenofovir or Entecovir
  - Emtricitabine/Tenofovir

HBIG IMMUNE PROPHYLAXIS

HBIG binds HBV
Prevents infection of hepatocytes

HBV Extra-hepatic Reservoir

HBIG
LIVER TRANSPLANTATION FOR HBV SURVIVAL AND HBIG THERAPY

Survival (%)

MONTHS

D Samuel et al.
N Eng J Med 1993;

LIVER TRANSPLANTATION FOR HBV PREVENTION OF RECURRENCE

ALT (IU/ml)

Months

HBIG
Lamivudine
Emtricitabine/Tenofovir

Pt: TW
HBsAg (+)
HBeAg (+)
HBVDNA (+)

HBsAg
HBV DNA

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EMTRICITABINE/TENOFOVIR PREVENTS POST-LT HBV

- N=21
- Receiving HBIG and HBV DNA undetectable
- Emtricitabine/Tenofovir started
- HBIG stopped
- 20/21 remained HBV DNA undetectable
- 1 patient who could not afford Emtricitabine/Tenofovir developed recurrent HBV DNA. Became HBV DNA undetectable when Emtricitabine/Tenofovir added
- 2/21 (12%) had persistence of anti-S

RT Stravitz et al
Liver Int 2012; 32:1138-1145.

LIVER TRANSPLANTATION HEPATITIS C VIRUS

- Hepatitis C is the single most common indication for liver transplantation
- Accounts for 40-45% of persons
- Recurs in virtually all patients
- Accelerated fibrosis progression
- 30% of patients develop cirrhosis within 5 years
SOFOSBUVIR AND RBV PRE-LIVER TRANSPLANT

• SOF+RBV initiated prior to undergoing LT
• All patients had HCC with MELD exception
• Treatment continued up until the time of LT

<table>
<thead>
<tr>
<th>N</th>
<th>61</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>59 years (46-73)</td>
</tr>
<tr>
<td>Male</td>
<td>80%</td>
</tr>
<tr>
<td>Caucasian</td>
<td>90%</td>
</tr>
<tr>
<td>HCV genotype: 1A, 1B, 2, 3</td>
<td>39%, 34%, 13%, 12%</td>
</tr>
<tr>
<td>IL28B non-CC</td>
<td>78%</td>
</tr>
<tr>
<td>Median MELD</td>
<td>8 (6-14)</td>
</tr>
<tr>
<td>Previous HCV treatment</td>
<td>75%</td>
</tr>
</tbody>
</table>

MP Curry et al. AASLD 2013

SOFOSBUVIR AND RIBAVIRIN PRE-LT TREATMENT

UD at LT

SVR Post-LT

< 30 days SVR when HCV RNA UD at LT

> 30 days

% of Patients

0 20 40 60 80 100

UD at LT SVR Post -LT < 30 days SVR when HCV RNA UD at LT > 30 days

MP Curry et al. AASLD 2013
**SOFOSBUVIR AND RIBAVIRIN POST-LT SEVERE HCV**

<table>
<thead>
<tr>
<th>Date</th>
<th>CMV</th>
<th>LBX</th>
<th>HVPG</th>
<th>SOF/RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>5/11</td>
<td>LT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8/11</td>
<td>+++</td>
<td>CMV/HCV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/12</td>
<td>+/-</td>
<td>IF 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9/12</td>
<td>+/-</td>
<td>IF 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12/12</td>
<td>+/-</td>
<td>IF 4</td>
<td>15</td>
<td>Start</td>
</tr>
<tr>
<td>3/13</td>
<td>+/-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4/13</td>
<td>Last para</td>
<td>Neg</td>
<td></td>
<td>HCV RNA (-)</td>
</tr>
<tr>
<td>6/13</td>
<td>No ascites</td>
<td>Neg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8/13</td>
<td>Neg</td>
<td>IF 2</td>
<td>10</td>
<td>HCV RNA (-)</td>
</tr>
<tr>
<td>10/13</td>
<td>Neg</td>
<td></td>
<td></td>
<td>Stop</td>
</tr>
<tr>
<td>11/13</td>
<td>Neg</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**SOFOSBUVIR AND RIBAVIRIN POST-LT SEVERE HCV**

<table>
<thead>
<tr>
<th></th>
<th>SOF+RBV</th>
<th>SOF+PEGINF+RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>32%</td>
<td>12</td>
</tr>
<tr>
<td>Mean time from LT (mos)</td>
<td>40 (3-178)</td>
<td>31 (5-124)</td>
</tr>
<tr>
<td>FCH</td>
<td>47%</td>
<td>33%</td>
</tr>
<tr>
<td>Week 4</td>
<td>69%</td>
<td>67%</td>
</tr>
<tr>
<td>Week 12</td>
<td>91%</td>
<td>75%</td>
</tr>
<tr>
<td>Week 24</td>
<td>83%</td>
<td>64%</td>
</tr>
<tr>
<td>EOT (last on tx)</td>
<td>100%</td>
<td>87%</td>
</tr>
<tr>
<td>SVR12</td>
<td>60%</td>
<td>50%</td>
</tr>
<tr>
<td>Death</td>
<td>30%</td>
<td>13%</td>
</tr>
</tbody>
</table>

X Forns et al
AASLD 2013

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17
SOFOSBUVIR AND RBV POST-LT HCV

<table>
<thead>
<tr>
<th>N</th>
<th>40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>59 years (49-75)</td>
</tr>
<tr>
<td>Male</td>
<td>78%</td>
</tr>
<tr>
<td>Caucasian</td>
<td>85%</td>
</tr>
<tr>
<td>HCV genotype: 1A, 1B, 2, 3</td>
<td>55%, 28%, 0%, 15%</td>
</tr>
<tr>
<td>IL28B non-CC</td>
<td>68%</td>
</tr>
<tr>
<td>HCV RNA (IU/ml)</td>
<td>6.55</td>
</tr>
<tr>
<td>Previous HCV treatment</td>
<td>88%</td>
</tr>
<tr>
<td>Mean time since LT</td>
<td>4.3 years (6-150 mos)</td>
</tr>
<tr>
<td>Tacrolimus, Cyclosporin</td>
<td>70%, 25%</td>
</tr>
</tbody>
</table>

SVR (%)

M Charlton et al.
AASLD 2013

ABT450/r-OMBITASVIR-DASABUVIR-RBV POST-LT HCV

- Single arm study
- LT > 12 months before enrollment
- 24 weeks of treatment
- Stage F0-F2
- Reduce dose of immune suppression
  - TAC: 0.5 mg Q week
  - CyA: 20% of pre-treatment dose

P Kwo et al.
EASL 2014.
ABT450/r-OMBITASVIR-DASABUVIR-RBV POST-LT HCV

N 34
Time since LT 48 months
Male 79%
Caucasian 85%
Mean age 60 years
IL28B non-CC 77%
Mean Log HCV RNA 6.6 IU/ml
Tacrolimus 85%
Mean creatinine 1.1 mg/dl

P Kwo et al. EASL 2014.

NEED FOR LIVER TRANSPLANT IMPACT OF ANTI-VIRAL TREATMENT


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LIVER TRANSPLANT
INTERACTING WITH THE LT CENTER

The Past:
Patients referred to LT center.
Never come back to GI practice.

The Future:
GI MD participates in patient management
Can conduct many of the LT evaluation tests locally
Can treat liver cancer
Can manage immune suppression