How to manage your patient with cirrhosis

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Objectives

- What we will review:
  - Diagnosis of cirrhosis
    - What do I do with this patient?
  - Brief review of MELD management
    - When do I refer to LT?
  - Special needs in the LTx candidate
    - General Medical
    - Disease Specific Issues
    - Cirrhosis Related Issues
Medical Management
Cirrhosis in Primary Care

Pointers to cirrhosis

- History
  - EtOH
  - IVDU
  - Endemic disease
- Family Hx
  - Autoimmune diseases
  - Metabolic d/o
Physical Exam clues

Neuro findings
- Asterixis
- Decreased cognition

Abdominal/Genitourinary
- Prominent abdominal collaterals
- Hepatosplenomegaly
- Cruveilhier Baumgarten murmur
- Ascites
- Anasarca
- Testicular atrophy

Cutaneous Findings
- Jaundice
- Spider angiomata
- Palmar erythema
- Terry’s nails

Miscellaneous
- Scleral icterus
- Gynecomastia
- Dupuytren contracture
- Muscle wasting
- Easy bruising
- Fetor hepatis
Laboratory Findings

- Platelet count < 160,000/L
- Elevated prothrombin time (INR)
- Elevated bilirubin
- Decreased albumin
- Normal or elevated aminotransferases
How do I settle this?

- Imaging
  - MRI or CT
  - US
  - Combination may be very valuable
- Liver biopsy
  - When is it needed?
  - AIH, HCC, HFE HHC
## Medications alerts

<table>
<thead>
<tr>
<th>Agent/class</th>
<th>Safe</th>
<th>Use w/ caution</th>
<th>Contraindicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAID</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>APAP</td>
<td></td>
<td>Up to 4g/d</td>
<td></td>
</tr>
<tr>
<td>Disulfiram</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Metformin</td>
<td></td>
<td>Beware of LA</td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPIs</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>B blockers</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Herbals</td>
<td></td>
<td></td>
<td>? unknowns</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Spironolactone</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
Procedures

- Always proceed with caution
- Realize that nobody can “clear” pts for surgery
  - One can only minimize risks
- Procedures that are OK:
  - Endoscopy
  - LV Paracentesis
  - Dental surgery
- Use a risk predictor
  - Go to Google and type Mayo Clinic end-stage-liver disease
Post-operative Mortality Risk in Patients with Cirrhosis

This calculator is intended for use by health care providers. The results of this tool should never be used alone to determine a patient's medical treatment. This tool is a statistical model and is not a substitute for an individual treatment plan developed by a doctor with personal knowledge of a specific patient. Other important factors that must be considered include the patient's own medical history and the experience, knowledge and training of the doctor. Doctors should personally discuss these results with patients when presenting prognoses or treatment recommendations.

To determine the risk of post-operative mortality for all types of major surgery, especially gastro-intestinal, orthopedic and cardiac surgery (includes open-heart procedures), please enter the following variables:

- What is the age? 65
- What is the ASA score? 3
  - Enter 3 for compensated cirrhosis
  - Enter 4 for decompensated cirrhosis
- What is the bilirubin? 4.5 (mg/dl)
- What is the creatinine? 1.6 (mg/dl)
- What is the INR? 1.3
- What is the etiology of cirrhosis? □ Alcoholic or Cholestatic
  □ Viral/Other

[Compute]
### Post-operative Mortality Risk in Patients with Cirrhosis

<table>
<thead>
<tr>
<th>Probability of Mortality</th>
<th>7 days</th>
<th>30 days</th>
<th>90 days</th>
<th>1 year</th>
<th>5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.284 %</td>
<td>12.805 %</td>
<td>19.853 %</td>
<td>36.287 %</td>
<td>71.299 %</td>
</tr>
</tbody>
</table>
Medical Management

Don’t forget the usual suspects:

- Diabetes
- Obesity
- Addiction
- Hypertension
- Depression
Vaccination Guidelines

http://www.a-s-t.org/mobile/Vaccinations.html
## Why vaccinate?

<table>
<thead>
<tr>
<th>Disease</th>
<th>Year Introduced</th>
<th>Cases</th>
<th>Deaths</th>
<th>Cases in 2002</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV</td>
<td>1989</td>
<td>132000</td>
<td>5820</td>
<td>7996</td>
</tr>
<tr>
<td>HiB</td>
<td>1986</td>
<td>13014</td>
<td>531</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8676</td>
<td>354</td>
<td></td>
</tr>
<tr>
<td>Polio</td>
<td>1954</td>
<td>18305</td>
<td>380</td>
<td>0</td>
</tr>
<tr>
<td>Measles</td>
<td>1964</td>
<td>458083</td>
<td>380</td>
<td>26</td>
</tr>
<tr>
<td>Rubella</td>
<td>1970</td>
<td>57686</td>
<td>18</td>
<td></td>
</tr>
</tbody>
</table>
Vaccination:
What do cirrhotic patients need?

- For the purposes of discussion:
  - Cirrhotic patients awaiting LT
    - Need prevention of hepatitis, pneumonia (influenza)
    - If splenectomy is to be considered asplenic prevention
    - Give vaccines early, before IS
Main Practical Point

- Vaccinate as early as possible:
  - Response rates **MUCH** better
General Practical Points

- **Review** vaccination status during first visit
- **Recheck** vaccination at referral to LT
- **Review** immunization status of household
- Any *live* vaccines **before** transplant
- Clinic staff and household members should receive influenza vaccine yearly
Hepatitis A Virus
The Pre-Liver Transplant Pt
Hepatitis A

- There is strong evidence that in face of acute HAV:
  - Chronic HBV can be made worse
    - HBsAg+ older patients
    - Advanced disease
  - HCV infected patients may have increased risk of FHF or death
  - Patients with other causes for ESLD may have worse outcome
# HAV vaccine Effectiveness

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count</th>
<th>Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLD</td>
<td>220</td>
<td>95-98%</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>49</td>
<td>98%</td>
</tr>
<tr>
<td>Decompensated Cirrhosis</td>
<td>121</td>
<td>50-65%</td>
</tr>
<tr>
<td>Liver Transplant</td>
<td>45</td>
<td>0-25%</td>
</tr>
</tbody>
</table>
Hepatitis B Virus
## HBV vaccine response

<table>
<thead>
<tr>
<th>Liver disease</th>
<th>Number</th>
<th>Dose (mcg)</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral disease</td>
<td>116</td>
<td>20-10</td>
<td>70-100%</td>
</tr>
<tr>
<td>ALD</td>
<td>103</td>
<td>20-40</td>
<td>20-75</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>23</td>
<td>20-40</td>
<td>20-70</td>
</tr>
</tbody>
</table>
Vaccination of the pt with cirrhosis HBV

CLD Patient

Serologies

HBsAg+ or HBsAb
- No vaccination
- Infected/immune

HBcAb
- Role for amnesic response

Seronegative
- Begin rapid vaccination
- Repeat if not effective
Pneumococcal Vaccine

- Data from the late 80’s shows increased risk of S. pneumoniae disease in cirrhotics
- Many states mandate and allow non-MD order of Pneumococcal vaccine in adults above 60-65
- Recommendations by ACIP stand for vaccination
Strategy for LT clinic

- Review pneumococcal vaccine
- Ensure that asplenic patients are vaccinated
- Consider boost for patients not vaccinated for >5yrs
Influenza A
Influenza A

- Heightened attention has been paid to Influenza A in CLD
  - Preventable
  - Treatable
  - Reported to cause extra-pulmonary disease in patients with CLD
    - Liver failure
    - Myositis/Myocarditis
Influenza A

- **Cirrhotics:**
  - 20 patients compared with 8 normal controls
  - 75-85% seroconversion (to each of 3 antigens)
  - Minimal side effects

- **LT recipients:**
  - 68% respond to one dose, >80% to two doses
Strategy for LT clinic

- **At start of influenza season:**
  - Vaccinate staff and families
  - Vaccinate all candidates and recipients
- Educate staff and patients about disease manifestations
- Have plan to **detect** and **treat** Influenza A
Liver Transplantation

**Indications**
- Cirrhosis - all causes
- Intrahepatic malignancy
- Acute liver failure
- Metabolic disease

**Contraindications**
- Extrahepatic malignancy
- Active infection
- Active substance abuse
- Severe co-morbidities
Model for End-Stage Liver Disease (MELD)

- Mathematical survival model created from data on patients undergoing TIPS
- MELD score estimates risk of 3-month mortality
  - Introduced formally in 2002
- Uses 3 objective laboratory values
  - Serum total bilirubin
  - Serum creatinine
  - INR
- In 2016 Na modifier added
Calculating MELD Scores

**The formula:**

\[
\text{MELD} = 0.957 \times \log_e(\text{creatinine mg/dL}) + 0.378 \times \log_e(\text{bilirubin mg/dL}) + 1.120 \times \log_e(\text{INR}) + 0.643
\]

\[
\text{MELD}_\text{Na} = \text{MELD}(i) + 1.32^* (137 - \text{Na}) - [0.033^* \text{MELD}(i)*(137 - \text{Na})]
\]

**Internet MELD calculator**

https://optn.transplant.hrsa.gov/resources/allocation-calculators/meld-calculator/
Organ Allocation for Liver Transplant

- Fulminant hepatic failure has highest priority
- MELD score determines priority in cirrhosis
  - Amongst patients with same blood type, highest MELD score determines priority
  - Waiting time used only to break ties with identical MELD scores
  - MELD scores are updated at regular intervals
MELD Exceptions

- **Hepatocellular carcinoma** (HCC) with one lesion between 2 - 5 cm or two to three lesions <3 cm (Milan criteria)
- **Hepatopulmonary syndrome** with PaO\(_2\) <60 mmHg on room air.
- **Portopulmonary hypertension**, with mean pulmonary artery pressure (mPAP) >25 mmHg at rest but maintained <35 mmHg with treatment.
- **Hepatic artery thrombosis** 7–14 days post-liver transplantation.
- **Familial amyloid polyneuropathy**, as diagnosed by identification of the transthyretin (TTR)
- **Primary hyperoxaluria** with evidence of alanine glyoxylate aminotransferase deficiency (these patients require combined liver-kidney transplantation).
- **Cystic fibrosis** with FEV1 (forced expiratory volume in 1 second) <40%.
- **Hilar cholangiocarcinoma**
MELD and Survival on Transplant Waiting List

- Probability of survival (%)
  - Months from listing
  - 0 2 4 6 8 10 12
  - 100 92.3% 90.7% 66.0% 33.8% <15 15 - 20 20 - 29 30+

- MELD AND SURVIVAL ON TRANSPLANT WAITING LIST
## Relationship Between CTP Score, MELD Score and 3-Month Mortality - UNOS Waiting List 2001

<table>
<thead>
<tr>
<th>Score</th>
<th>Patients (n)</th>
<th>Mortality %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MELD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;9</td>
<td>124</td>
<td>1.9</td>
</tr>
<tr>
<td>10-19</td>
<td>1800</td>
<td>6.0</td>
</tr>
<tr>
<td>20-29</td>
<td>1098</td>
<td>19.6</td>
</tr>
<tr>
<td>30-39</td>
<td>295</td>
<td>52.6</td>
</tr>
<tr>
<td>&gt;40</td>
<td>120</td>
<td>71.3</td>
</tr>
<tr>
<td><strong>CTP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7-9</td>
<td>318</td>
<td>4.3</td>
</tr>
<tr>
<td>10-12</td>
<td>2357</td>
<td>11.2</td>
</tr>
<tr>
<td>13-15</td>
<td>588</td>
<td>40.1</td>
</tr>
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</table>
# MELD Score and Risk of Death Awaiting Liver Transplantation

<table>
<thead>
<tr>
<th>MELD</th>
<th>RR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 -10</td>
<td>0.32</td>
<td>p &lt;0.001</td>
</tr>
<tr>
<td>11-20</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>21-30</td>
<td>8.07</td>
<td>p &lt;0.001</td>
</tr>
<tr>
<td>31-40</td>
<td>35.50</td>
<td>p &lt;0.001</td>
</tr>
</tbody>
</table>

- Mortality rates per 1000 patients
- MELD categories: 6-11, 12-14, 15-17, 17-20, 21-23, 24-26, 27-29, 30-39, 40+

Hazard ratios (HR) and p-values:
- HR=3.64, P<0.001
- HR=2.35, P<0.001
- HR=1.21, P=0.41
- HR=0.62, P<0.01
- HR=0.38, P<0.001
- HR=0.22, P<0.001
- HR=0.18, P<0.001
- HR=0.07, P<0.001
- HR=0.04, P<0.001

HR=hazard ratio
How to manage the MELD

- Assessment is required at least at 3 mo intervals for least sick
- Weekly updates for sicker patients
- When there is acute decompensation need to notify LT center
- Labwork for updates should be performed on same day
Disease Specific Issues

- Viral Diseases
  - HCV
  - HBV
- Cholestatic disorders
- PSE
- Alcoholic liver disease
- Hemochromatosis
Disease Specific Issues

- **HCV**
- Patients with low MELD should be considered for DAA tx
  - As MELD rises, HCV+ organs increase the likelihood of LT
- Aggressive HCC screening (CT q6mo)
- Vaccinate against HAV/HBV
Disease Specific Issues

- **HBV**
  - If viral replication ongoing, anti-virals are needed
  - Close monitoring for YMDD mutations, drug toxicity
- Aggressive HCC screening
- Discuss prophylaxis after LT with patient
Disease Specific Issues

- Cholestatic disorders
  - Assess bone mineral density
    - Supplement Vit D and Calcium
    - If biphosphonates needed, use I.V.
  - Assess and treat pruritus
- Consider ursodeoxycholic acid
Disease Specific Issues

- Primary Sclerosing Cholangitis
  - ERCP for tight strictures
  - Aggressive screening for CholangioCA
  - Consider accelerated Colon CA screen for those patients with ulcerative colitis
- Ursodeoxycholic acid may help with symptoms
Disease Specific Issues

- Alcoholic liver disease
- Most programs require 6 mo sobriety
  - Consider alcohol contract
  - Enforce screening for alcohol use
- Patients always at risk for recurrence
- Smokers may be at higher risk for squamous cell CA.
Disease Specific Issues

- Hemochromatosis
- Phlebotomy schedule should be continued if safe
- Monitor for cardiovascular effects
  - Myopathy
  - Conduction problems
- Aggressive HCC screening
Issues Common to all Cirrhotics
Natural History of Chronic Liver Disease

Development of cirrhosis

Chronic liver disease ➔ Compensated cirrhosis ➔ Development of complications:
- Variceal hemorrhage
- Ascites
- Encephalopathy
- Jaundice ➔ Decompensated cirrhosis ➔ Median survival ~ 1.6 years ➔ Death

Median survival
- Compensated cirrhosis: ~ 9 years
- Decompensated cirrhosis: ~ 1.6 years

Orthotopic liver transplant (OLT)
<table>
<thead>
<tr>
<th>Condition</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compensated Cirrhosis</td>
<td>9 yrs</td>
</tr>
<tr>
<td>Decompensated Cirrhosis</td>
<td>1.6 yrs</td>
</tr>
<tr>
<td>Hepatopulmonary syndrome</td>
<td>10 mos</td>
</tr>
<tr>
<td>Spontaneous bacterial peritonitis</td>
<td>9 mos</td>
</tr>
<tr>
<td>Hepatorenal syndrome</td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>6 mos</td>
</tr>
<tr>
<td>Type 2</td>
<td>2 wks</td>
</tr>
</tbody>
</table>
Decompensation Shortens Survival

Gines et. al., Hepatology 1987;7:122
Development of Complications in Compensated Cirrhosis

- Ascites
- Jaundice
- Encephalopathy
- GI hemorrhage

Probability of developing event

Gines et. al., Hepatology 1987; 7:122
VARICES
Varices Increase in Diameter Progressively

Rate of progression stage to stage: 7-8%/year

Merli et al. J Hepatol 2003;38:266
Prevalence of Esophageal Varices in Cirrhosis

Pagliaro et al., In: Portal Hypertension: Pathophysiology and Management, 1994: 72
Treatment of Varices / Variceal Hemorrhage

No varices

Varices
No hemorrhage

Variceal hemorrhage

Recurrent hemorrhage

No specific therapy
Repeat endoscopy in 2-3 yrs*

* Sooner with cirrhosis decompensation
Treatment of Varices / Variceal Hemorrhage

- No varices
- Varices
  - No hemorrhage
  - Variceal hemorrhage
    - Recurrent hemorrhage

Prevention of first variceal hemorrhage
Prevention of First Variceal Hemorrhage

- Porto-caval shunt
- β-blockers
- Sclerotherapy

D’Amico et al., Hepatology 1995; 22;332
# Non-Selective Beta-Blockers Prevent First Variceal Hemorrhage

<table>
<thead>
<tr>
<th>Variceal Size</th>
<th>Control</th>
<th>Beta-blocker</th>
<th>Absolute Rate Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>All varices</td>
<td>25%</td>
<td>15%</td>
<td>-10% (−16 to −5)</td>
</tr>
<tr>
<td>(11 trials)</td>
<td>(n=600)</td>
<td>(n=590)</td>
<td></td>
</tr>
<tr>
<td>Large varices</td>
<td>30%</td>
<td>14%</td>
<td>-16% (−24 to −8)</td>
</tr>
<tr>
<td>(8 trials)</td>
<td>(n=411)</td>
<td>(n=400)</td>
<td></td>
</tr>
<tr>
<td>Small varices</td>
<td>7%</td>
<td>2%</td>
<td>-5% (−11 to 2)</td>
</tr>
<tr>
<td>(3 trials)</td>
<td>(n=100)</td>
<td>(n=91)</td>
<td></td>
</tr>
</tbody>
</table>

*D’Amico et al., Sem Liv Dis 1999; 19:475*
The Risk of First Bleeding is Not Reduced by Adding Isosorbide Mononitrate (ISMN) to β-blockers

Free of a first variceal bleeding

Survival

García-Pagán et al., Hepatology 2003; 37:1260
Isosorbide Mononitrate (ISMN) is Not Useful to Prevent First Variceal Bleed in Patients with Contraindications to β-blockers

García-Pagán et al., Gastroenterology 2001; 121:908
Variceal Band Ligation (VBL) vs. Beta-Blockers (BB) in the Prevention of First Variceal Bleed

Treatment of Varices / Variceal Hemorrhage

- **No varices**
- **Small varices**
  - No hemorrhage
  - Repeat endoscopy in 1-2 years*
  - Beta-blockers?
- **Medium/large varices**
  - No hemorrhage
- **Variceal hemorrhage**
- **Recurrent hemorrhage**

*Sooner with cirrhosis decompensation
Treatment of Varices / Variceal Hemorrhage

No varices

Small varices
No hemorrhage

Medium/ large varices
No hemorrhage

Variceal hemorrhage

Recurrent hemorrhage

1) β-blockers (propranolol, nadolol) indefinitely
2) Endoscopic variceal ligation in patients intolerant to β-blockers
Polytetrafluoroethylene-covered TIPS stents
Covered Stents Are More Likely to Remain Functional Than Uncovered Stents

\[ \text{% free of shunt dysfunction} \]

- **Covered**
- **Uncovered**

\[ p = 0.0005 \]

Bureau et al. Gastroenterology 2004; 126:469
Management of Ascites

Chronic liver disease → Compensated cirrhosis → Decompensated cirrhosis → Death

Ascites

Diagnosis:
- Clinical
- US or CAT scan

Treatment:
- Spironolactone-based
- No NSAIDs

Early diagnosis of SBP:
- Paracentesis q admission or with symptoms
- Avoid aminoglycosides

Orthotopic liver transplant (OLT)
Natural History of Ascites

Portal Hypertension
No Ascites

Uncomplicated
Ascites

Hepatorenal
Syndrome

HVPG < 10 mmHg
Mild Vasodilation

HVPG > 10 mmHg
Moderate Vasodilation

HVPG > 10 mmHg
Severe Vasodilation

HVPG > 10 mmHg
Extreme Vasodilation
Initial Workup of Ascites
Diagnostic Paracentesis

Routine
- PMN count
- Culture
- Protein/Albumin
- ? cirrhotic ascites
- ? secondary infection
- ? SBP
- Glucose, LDH

Optional
- Amylase
- Cytology
- ? pancreatic ascites
- ? malignant ascites
- ? secondary infection
- ? cirrhotic ascites
Ascites Fluid Analysis

Routine
- Albumin
- Protein
- PMN cell count
- Cultures

Optional
- Glucose
- LDH
- Amylase
- Red blood cell count
- TB smear and culture
- Cytology
- Triglycerides
Ascites Can Be Characterized by Serum-Ascites Albumin Gradient (SAAG) and Ascites Protein

Source of ascites

Hepatic sinusoids

SAAG > 1.1

“Capillarized” sinusoid
Ascites protein < 2.5

Sinusoidal hypertension
- Cirrhosis
- Late Budd-Chiari

Normal “leaky” sinusoid
Ascites protein > 2.5

Post-sinusoidal hypertension
- Cardiac ascites
- Early Budd-Chiari
- Veno-occlusive disease

Peritoneum

SAAG < 1.1

Peritoneal lymph
Ascites protein > 2.5

Peritoneal pathology
- Malignancy
- Tuberculosis
Serum-Ascites Albumin Gradient and Ascites Protein Levels in the Most Common Causes of Ascites

Diagnosis:
- Liver biopsy
- Clinical/LSS

Screen for varices (EGD):
- Large varices → beta-blockers
- Small varices → EGD in 1-2 yrs
- No varices → EGD in 2-3 yrs

Screen for HCC:
- Imaging and AFP q 6 mos

Measures to stop alcohol use
- Vaccination

Orthotopic liver transplant (OLT)
Death
Questions?
vargas.hugo@mayo.edu