Learning Objectives: Cirrhosis

- Identify and treat /prevent cirrhosis or its progression (mx etiology).
- Preventive measures:
  - Vaccinations
  - Nutrition
  - Cancer screening/surveillance
- Manage key complications:
  - Ascites
  - Renal failure
  - Hepatic encephalopathy
  - Infection
  - HCC
  - Varices
- Transplant indications and assessment.
Cirrhosis is end stage of chronic liver disease of different etiologies

- HCV, Alcohol NASH most common
- Characterized by bridging fibrosis and nodules in biopsy
- Compensated cirrhosis may be asymptomatic
- Decompensated disease has 50-80% 5 year mortality
- 12th most common cause of death in US
- Rising burden: HCV, HCC, Obesity
Suspect CLD if LFTs are abnormal or Risk Factors are present

- Alcohol
- Obesity
- Percutaneous exposure to blood.
  - Birth Cohort
  - Blood products < 1992,
  - Tattoos,
  - Clotting factors < 1987,
  - Hemodialysis,
  - Needle sticks in HCW,
  - Shared needles with Injection drug use,
  - Shared straws with nasal drug use,
  - Incarceration,
  - health care with poor infection control
- HBV: Endemic areas
Identifying Cirrhosis in Primary Care Setting

- Early cirrhosis is asymptomatic
- Suspect Liver disease/cirrhosis if
  - there are risk factors (Alcohol, Viral, Metabolic syndrome, FH)
  - Spider nevi, palmar erythema, Terry’s nails, gynecomastia, Dupeytrens contractures, firm sharp edged liver, splenomegaly.
  - Persistently abnormal liver tests (especially AST > ALT)
  - LOW PLATELETS
Establish Cirrhosis with Liver Biopsy (specialist/Radiology) or Non-invasively

• Liver BX is invasive, costly, with risk and poorly accepted

• Alternatives to liver Bx:
  • APRI score = \(\frac{AST}{40}/Plts \times 100\)
  • Fib-4 score = \(\frac{AST \times Age}{Plts \times \sqrt{ALT}}\)
  • Fibrosure – blood test
  • Fibroscan: blind elastic recoil US
  • US (enhanced shear wave) – augmented U/S test
  • MRE – Magnetic Resonance Elastography

• Stage 3-4 fibrosis /cirrhosis Rule of 12:
  • Spleen > 12 cm
  • Portal Vein > 12 mm
  • Platelets < 12^2 (144)
Initial Management of the Cirrhotic Patient Includes General Health, Education and Secondary Prevention

1. Identify and Treat Etiology
2. Identify and manage co-mobidities that may lead to progression (alcohol, HIV, obesity)
3. Health education and secondary prevention. (HBV, HCV, Genetic etc)
4. Vaccination against flu and pneumonia, hepatitis A and B virus
5. Treat associated conditions (nutrition, diabetes, osteoporosis, malnutrition.)
   • Promote family and cohabitants’ participation to primary prevention and help remove barriers/impediments to transplant
     • substance dependence
     • Social support
   • Identify and correct medical issues
Education and intervention to reduce progression

1. Establish etiology and comorbidities (HIV HBV HCV)
2. Abstinence /cessation of alcohol consumption
3. Obesity
4. Establish degree of fibrosis to determine the need for initiating additional screening measures (eg, hepatocellular carcinoma [HCC] screening).
5. Make sure patient is treated for any treatable etiology (refer, if you do not treat)
Treating the Disease May Reverse Cirrhosis or Stop Progression

530 patients with advanced fibrosis, treated with interferon-based therapy, and followed for 8.4 (IQR 6.4-11.4) years

Fibrosis reduced on Serial biopsy on Treating Hepatitis B
Treat Cause of Liver Disease

- Alcoholic liver disease
- Hepatitis B: Tenofovir, entecavir.
- Treat HCV: Oral, non Interferon based treatments
- Autoimmune hepatitis
- Hemochromatosis: phlebotomy.
- PBC: Urso/budesonide/MTX

Important to establish the diagnosis accurately wherever possible
General Measures

• Manage Substance dependence:

• Obesity

• Social: Caregiver support: especially for hepatic encephalopathy

• Debility: conditioning (physical therapy)
General Measures: Immunizations and Nutrition

- Cirrhotic patients are immune compromised and have special vaccination requirements (same as >65)
  - Hepatitis A
  - Hepatitis B
  - Pneumococcal: PCovjugateV13 or PPolysaccherideV23 should receive a single dose of PCV13 followed by a dose of PPSV23 at least 8 weeks later. PPSV23, at least 5 years after the most recent dose of PPSV23.
  - Annual Influenza

(http://www.cdc.gov/vaccines/schedules/hcp/imz/adult-conditions.html accessed 4/14/15)
Cirrhosis: Protein Calorie and Micronutrient deficiency, and Catabolic in Post-Absorptive State

- Frequent small meals
- Do not skip meals
- Bedtime ensure Plus or snack
- Protein: 1-2 g/kg BW
  Do Not restrict for HE.
- Na restriction < 2000mg/d for ascites
- Fluid Restriction if dilutional hyponatremia

Improved Total Body Protein with 16oz Ensure+ (474 cc, 26g protein 710 kcal)

Lindsay D. Plank et al Nocturnal Nutritional Supplementation Improves Total Body Protein Status of patients with Liver Cirrhosis: a Randomized 12-Month Trial HEPATOLOGY 2008;48: 557-566
HCC Surveillance  Every 6 months (US and AFP)- 3-5% Annual HCC Incidence in Cirrhosis

<table>
<thead>
<tr>
<th>HCC screening in Cirrhosis</th>
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<tbody>
<tr>
<td><strong>High Risk</strong></td>
<td><strong>Moderate Risk</strong></td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>PSC</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>Alpha-1</td>
</tr>
<tr>
<td>Alcoholic</td>
<td>Autoimmune</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>Wilson’s</td>
</tr>
<tr>
<td>Non-ALD steatohepatitis</td>
<td>PBC</td>
</tr>
<tr>
<td>On Waiting list</td>
<td></td>
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</tbody>
</table>

- **No cirrhosis:**
  - Chronic hepatitis B carriers: males aged 40 y and females aged 50 y
  - family history of hepatocellular cancer in chronic hepatitis B.
Surveillance algorithm

**Figure.** A proposed liver ultrasound algorithm for surveillance of hepatocellular carcinoma.


Gish, R., Gastroenterology & Hepatology, 2014; 10;2:121-123.
Prognosis: MELD and Child Score

MELD Model for End Stage Liver Disease:
\[10 \times [0.957 \ln(\text{Creat} \text{[mg/dL]}) + 0.378 \ln(\text{Total Bili} \text{[mg/mL]}) + 1.120 \ln(\text{INR}) + 0.643]\]

Table 2: Child-Pugh scoring system for liver cirrhosis and related indication priority for transplantation

<table>
<thead>
<tr>
<th>Score</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>&lt; 2</td>
<td>2.3</td>
<td>&gt; 3</td>
</tr>
<tr>
<td>Prothrombin time (INR)</td>
<td>&lt; 4 sec. (&lt; 1.7)</td>
<td>4-6 sec. (1.7-2.3)</td>
<td>&gt; 6 sec. (&gt; 2.3)</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>&gt; 3.5</td>
<td>3.5-2.8</td>
<td>&lt; 2.8</td>
</tr>
<tr>
<td>Ascites</td>
<td>Absent</td>
<td>Mild</td>
<td>Severe</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>Absent</td>
<td>Mild</td>
<td>Severe</td>
</tr>
</tbody>
</table>

http://www.unos.org/resources/meldPeldCalculator.asp
Prognosis is Poor After Index Event: Liver Transplant Evaluation

- Liver transplant evaluation in all patients with decompensated liver disease (Child’s≥ B).
  - compensated cirrhosis: 91% 5 year survival.
  - If index event: (Bleed, ascites, HE, renal insufficiency): <50% 5yr survival

(Fattovich Gastro 97; 112: 463)
Absolute Contra-indications to TP: competing risks of Death

- Uncontrolled infection
- Extra-hepatic malignancy
- Active substance or alcohol dependence.
- Severe cardiopulmonary disease.
- Severe pulmonary hypertension.
- Inability to follow immunosuppressive therapy.
Relative Contra-indications: relatively competing risks of death

- Advanced Hepatocellular carcinoma (>Stage 3A)
- Cholangiocarcinoma (except stage 1)
- Advanced age (>70yrs)
- Portal vein thrombosis.
- Insufficient social support.
- HIV:
  - In selected HIV-infected recipients post transplant survival similar to that of HIV-negative recipients.
  - Survival without transplant worse
  - OLT considered if there is no history of opportunistic infections or neoplasms, CD4 cell count >100 cells/mm³, and plasma HIV viral load suppressible with antiretroviral treatment.
Treat Complications:

- Ascites
- Spontaneous Bacterial Peritonitis
- Varices/ prevent Hemorrhage
- Hepatic Encephalopathy
Ascites Management

- **Diagnostic paracentesis:** in every patient. (TP, Alb Cell Count Diff (Triglycerides)).
- **Dietary salt restriction** (Education)
  Fluid loss depends on negative sodium balance (water loss follows)
  - 2g sodium/day (88mmol)
- **Diuretics**
  - Spironolactone 100 – 300 (400) mg/day and
  - Furosemide 40-160 (240) mg/day
Large Volume Paracentesis

- Indications:
  - Discomfort.
  - Dyspnea.
  - Tense ascites (hemodynamic improvement).
  - Renal insufficiency (compartment syndrome).
  - Refractory ascites

- Up to 5 liters may be safely removed sans albumin. However, preferable to use 8g albumin IV per liter ascites removed.
PPS: Albumin Vs D70 Vs PGL

Percent Post paracentesis syndrome

PPS: Progressive rise in Renin and very high mortality

p<0.004

p<0.018

Albumin
Dextran70
Polygeline

PPS: Progressive rise in Renin and very high mortality
Refractory Ascites Equally Managed Using TIPS or Taps. Stop Beta Blockers.

Transjugular Intrahepatic Portosystemic shunting Versus Paracentesis Plus albumin for Refractory Ascites in Cirrhosis GINE’S.
GASTROENTEROLOGY 2002;123:1839–1847

The North American Study for the treatment of Refractory Ascites.
GASTROENTEROLOGY 2003;124:634–641

Sodium Restriction is for Hypervolemia, Water restriction is for Hyponatremia

- RAAS and increased aldosterone
- Urine [Na] < 70
  Na:K < 1

- Hyponatremia: hypervolemic dilutional due to AVP
- Restrict water for NA< 124.
Spontaneous Peritonitis

- **Often present with:**
  - Encephalopathy, GI bleeding, diarrhea, renal impairment, non-specific symptoms of infection.
- **May not have.**
  - Peritoneal signs, fever, pain.
- **Prognosis.**
  - 50% mortality in 1 year.
  - Two thirds have recurrence in 1 year.
- **DP:** admission, (in hospital for any deterioration or bleed)
<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymorphonuclear cell count</td>
<td>&gt; 500/mm³</td>
<td>SBP (97% specific)</td>
</tr>
<tr>
<td>Fluid culture (blood culture bottle)</td>
<td>Positive</td>
<td>SBP</td>
</tr>
</tbody>
</table>
SBP Treatment

- Antibiotics
- Albumin (1.5g/kg bw day 1, and 1g/kg bw day 3)
Treatment SBP: Antibiotics

- Empiric therapy initiated at time of diagnosis.
- Cefotaxime 2g q 8-12hrs. (Ceftriaxone protein bound diminished penetration)
- May narrow spectrum once sensitivities are available
- Treatment: 5 days (similar outcome to 10 day therapy)
SBP: Albumin 1.5g/kg D1; 1g/kg D3

![Bar chart showing comparison between No Alb and Albumin in Renal Imp, Death In Hosp, and 3m death with p-values P<0.002, P<0.01, P<0.03]

Sort, P. NEJM: 341 403-9
SBP Prophylaxis: Indications

• Previous episode of SBP (1 yr 40-70% recurrence)
• Ascites total protein < 1g/dl (20-40% incidence in 1 year)
• Bilirubin > 2.5 mg/dl (1 yr 43%)
• If NO prior SBP, alb>1g/dl and bili< 2.5: risk for SBP
  • 1 year 0%
  • 3 year 3%
SBP Prophylaxis

- Antibiotic choices (all given po)
  - Norfloxacin, 400mg/d; Fluoro-quinolone resistance possible: local resistance pattern
  - Trimethoprim-cotrimoxazole DS 5 days/week
- Meta-analysis: Survival advantage
- Life expectancy after SBP: 1 yr 30-50% 2yr 25-30%
Algorithm for Prevention of Variceal Hemorrhage in Cirrhosis

Diagnosis of Cirrhosis

Endoscopy

- No Varices
  - Follow-up EGD in 2-3 yrs*
- Small Varices
  - Follow-up EGD in 1-2 yrs*
- Medium/Large Varices
  - Beta-blocker# therapy
    - No Contraindications
      - Step-wise increase until maximally tolerated dose
      - Continue beta-blocker (life-long)
    - Contraindications or Beta-blocker intolerance
      - Endoscopic Variceal Band Ligation

*Every year in decompensated cirrhosis

#non-selective beta-blocker (propranolol, nadolol)

Antibiotic Choice in **GI Bleeder**

Antibiotic choice: IV gives better levels. Choice depends on likely organisms (resistance patterns etc.). Oral Norflox and Levoflox no longer antibiotics of choice.
Hepatic Encephalopathy

• A spectrum of reversible neuropsychiatric abnormalities in patients with liver disease\(^1,2\) or portosystemic shunting\(^3\)

• Symptoms may range from subtly altered mental status to deep coma\(^4,5\)

• Marked by alternating periods of acute exacerbation and remission\(^6\)

• Occurs in up to \(~50\%\)^7 to 70\%\(^8\) of patients with cirrhosis

Delirium or Neuropsychiatric Changes in Cirrhotic possibly dt Hepatic Encephalopathy

- Rule out other etiologies of delirium or coma (Alcohol, sedatives, Drugs, Electrolyte abnormalities, hypoglycemia, subdural hematoma, seizures)
- Establish precipitant
  - Hypovolemia, Hypokalemia (too much lactulose), infection, GI Bleed, Over diuresis, constipation, dietary protein excess (red meat)
- Supportive care (fall precautions, monitoring, IV fluids)
- Treat/remove precipitant
- Lactulose (Avoid overdosing: diarrhea is counter productive)
- Rifaximin 550 bid.
Minimal Hepatic Encephalopathy (Covert) does not have overt signs but is debilitating

- Combination of psychometric test (number connection tests (NCTs) A and B, the digit symbol test, and the block design test, computerized psychometry, critical flicker frequency test, inhibitory control.
- It is common and affects quality of life
- Increases risk of accidents.

Diagnosis MHE

- Combination of psychometric test (number connection tests (NCTs) A and B, the digit symbol test, and the block design test, computerized psychometry, critical flicker frequency test, inhibitory control.
- Abnormal tests predict impaired navigational skills in cirrhotic patients tested in a driving simulator.

Minimal Hepatic Encephalopathy increases Driving Risk and reduces QOL.

**Figure 2.** Reversal of minimal hepatic encephalopathy (MHE) after 2 and 8 weeks of treatment in both the groups. The percentage of patients showing reversal of MHE was significantly higher in the rifaximin group both at 2 weeks (57.1% (28/49) vs. 17.8% (8/45) in the placebo group; *P*<0.0001) and at 8 weeks (75.5% (37/49)) vs. 20% (9/45) in the placebo group; *P*<0.0001).

**Figure 3.** Sickness impact profile (SIP) scores of patients with and without minimal hepatic encephalopathy (MHE) (*P*<0.001 for comparison of all scores between the non-MHE group and MHE group (rifaximin and placebo)).
Treatment MHE

• Non-absorbable disaccharide lactulose and probiotics are effective. Antibiotics improve MHE.
• The non-absorbed and safe antibiotic rifaximin has now been shown to improve psychometric test performance scores and concomitantly improve HRQOL in patients with MHE.

Prasad S Lactulose improves cognitive functions and HRQOL in minimal hepatic encephalopathy. Hepatology 2007; 45: 549 – 59

Sidhu S. Rifaximin improves Psychometric Performance and Health Related Quality of Life in Patients with Minimal Hepatic Encephalopathy (The RIME trial). Am J Gastroenterol 2011; 106:307–16
THANK YOU.