CHRONIC LIVER DISEASE AND ITS COMPLICATIONS

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I have no disclosures relevant to this presentation.
Learning Objectives

• Natural history and outcome of cirrhosis

• Initial management of complications of cirrhosis

• Updates/Recent studies on management of complications of cirrhosis

• Appropriate timing of referral for liver transplantation
Natural History of Chronic Liver Disease

Chronic Liver Disease → Compensated Cirrhosis → Decompensated Cirrhosis → Death

Ascites
Jaundice
Encephalopathy
Variceal Hemorrhage
Probability of Hepatic Decompensation: 58% over 10 years

Hepatology 1987; 7: 122-128
Risk Factors for Hepatic Decompensation

- GI Bleeding
- Infection
- Alcohol intake
- Medications
- Dehydration
- Constipation
- Obesity (Hepatology 2011; 54: 555)
- Surgery
- Ongoing viral infection
Hepatic Decompensation Reduces Survival

Hepatology 1987; 7: 122-128
Prediction of 3-Month Survival in Cirrhotics

MELD score = 3.8 \ln (\text{bilirubin}) + 11.2 \ln (\text{INR}) + 9.6 \ln (\text{creatinine}) + 6
Prediction of 1 Year Survival in Cirrhotics: Child Turcotte Pugh Score

<table>
<thead>
<tr>
<th>Points</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalopathy</td>
<td>None</td>
<td>1 and 2</td>
<td>3 and 4</td>
</tr>
<tr>
<td>Ascites</td>
<td>Absent</td>
<td>Slight</td>
<td>Moderate</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>1-2</td>
<td>2-3</td>
<td>&gt;3</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.5</td>
<td>2.8-3.5</td>
<td>&lt;2.8</td>
</tr>
<tr>
<td>INR</td>
<td>&lt;1.7</td>
<td>1.7-2.3</td>
<td>&gt;2.3</td>
</tr>
</tbody>
</table>

- **5-6**  A  100%  1 year survival
- **7-9**  B  80%  1 year survival
- **10-15**  C  45%  1 year survival
Natural History of Cirrhotic Ascites

- Portal Hypertension
  - No Ascites

- Uncomplicated Ascites

- Ascites + Hyponatremia

- Refractory Ascites
Management of Ascites

- 50% of compensated cirrhotics will develop ascites 10 years from diagnosis
- Ascites most common complication of cirrhosis that leads to hospital admission
- New-onset ascites requires diagnostic paracentesis
- Bleeding complications in less 1/1,000 who require paracentesis
- Use of blood products (FFP/platelets) not data supported
- SAAG of $\geq 1.1$ is 97% accurate for portal hypertension

Treatment Options for Cirrhotics with Ascites

- Cessation of Alcohol use
- Sodium restricted diet (2000mg/day) and education
- Dual diuretics: Spironolactone and Furosemide, orally with single daily dosing
- Most patients do not need fluid restriction
- Ratio Spironolactone 100mg: Furosemide 40mg, increase every 3-5 days
- Maximum doses are Spironolactone 400mg: Furosemide 160mg
- Amiloride 10-40mg substituted for Spironolactone for tender gynecomastia
- Consider stopping NSAIDS, ACE Inhibitors, Angiotensin Receptor blockers, Propranolol
- Liver transplant evaluation
- Weekly albumin infusion in decompensated cirrhotics improves overall survival (ANSWER study)

Lancet 2018; 391: 2417-2429.
Management of Refractory Ascites

• 10% of cirrhotics with ascites

• Unresponsive to 2g sodium diet and high dose diuretics
  OR

• Clinically significant complications of diuretics (encephalopathy, creatinine > 2g/dL, sodium < 120 mmol/L, potassium > 6 mmol/L)

• Options include serial LVPs vs. TIPS → liver transplant

• In LVP ≥ 5L, albumin infusion of 6-8g/L removed improves survival and prevents post-paracentesis circulatory dysfunction

• Use of nonselective beta blockers in refractory ascites has conflicting data, but should be reduced or discontinued in SBP < 90mmHg, acute kidney injury

Hepatology 2010; 52: 1017-1022.
### Large Scale Randomized Controlled Trials of TIPS vs. LVP for Refractory Ascites

<table>
<thead>
<tr>
<th>N</th>
<th>Control of Ascites</th>
<th>Survival</th>
<th>Encephalopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>61% vs. 18% (p=.006)</td>
<td>69% vs. 52% (p=.11)</td>
<td>58% vs. 48%*</td>
</tr>
<tr>
<td>70</td>
<td>51% vs. 17% (p=.003)</td>
<td>41% vs. 35% (p=.29)</td>
<td>77% vs. 66%</td>
</tr>
<tr>
<td>109</td>
<td>58% vs. 16% (p&lt;.001)</td>
<td>40% vs. 37%*</td>
<td>60% vs. 34% (p=.058)</td>
</tr>
<tr>
<td>66</td>
<td>79% vs. 42% (p=.001)</td>
<td>77% vs. 52% (p=.021)</td>
<td>Severe (p=0.39)</td>
</tr>
</tbody>
</table>

* P value not significant.
Natural History of Cirrhotic Ascites

- Portal Hypertension
  - No Ascites
  - Uncomplicated Ascites
  - Ascites + Hyponatremia
  - Refractory Ascites
  - Hepatorenal Syndrome
Hepatorenal Syndrome – clinical features

- Cirrhosis with ascites
- Serum creatinine > 1.5mg/dL
- No creatinine improvement after 2 days diuretic withdrawal
- No creatinine improvement after volume expansion with albumin (1g/kg up to 100g)
- Absence of shock, nephrotoxins
- Bland urine sediment/no parenchymal kidney disease

Natural History of Hepatorenal Syndrome

**Type 2 HRS**

- Therapeutic paracenteses
- Cefotaxime

**Type 1 HRS**

- SBP

Creatinine (mg/dL)

- 0
- 1
- 2
- 3
- 4
- 5
- 6

Months

- 0
- 2
- 4
- 6

Weeks

- 0
- 1
- 2
- 3
Hepatorenal Syndrome – management

- Treatment of underlying liver disease (alcoholic hepatitis, HBV)
- Prevention with albumin infusion in SBP
- Cessation of nonselective beta blockers in SBP
- Albumin/Octreotide/Midodrine
- In ICU, Norepinephrine (or Vasopressin) + Albumin
- Terlipressin – not yet approved in U.S.
- Hemodialysis as bridge to liver recovery or transplant
- TIPS
- Liver transplantation
Natural History of Cirrhotic Ascites

- Portal Hypertension
  - No Ascites
- Uncomplicated Ascites
- Ascites + Hyponatremia
- Refractory Ascites
- Hepatorenal Syndrome
- SBP
Spontaneous Bacterial Peritonitis: Treatment

Systemic antibiotics for Community Acquired SBP
• Ceftriaxone or Cefotaxime
• Avoid aminoglycosides
• Most patients will respond to 5 day course of treatment

Cessation of nonselective beta blockers

Albumin IV on Day 1 and Day 3 with any of following:
• BUN > 30mg/dL
• Creatinine > 1.0 mg/dL
• Serum bilirubin > 4mg/dL

Gastroenterology 2014; 146: 1680-1690.
Spontaneous Bacterial Peritonitis: Primary & Secondary Prophylaxis

- Childs B or C cirrhotics hospitalized with GI bleeding (IV Ceftriaxone)

- Cirrhotics with ascites total protein <1g/dL hospitalized for something other than GI bleeding

- Ascites total protein <1.5g/dL AND Renal failure (Creatinine ≥ 1.2, BUN ≥ 25 or serum Na ≤ 130) OR Liver failure (Child score ≥ 9 or Bilirubin ≥ 3)

- Prior history of SBP

- Trimethoprim/Sulfa 1DS tablet daily, Ciprofloxacin 500mg daily

- Weekly dosing of antibiotics may be as effective as daily dosing, although concerns about resistance remain

Hepatology 2013; 57: 1651-1653
Am J Gastroenterology 2018; 1167-1176
Treatment of Hepatic Encephalopathy

- Determine precipitant of hepatic encephalopathy and treat (Infection, Electrolytes, GI Bleeding, Constipation, Dehydration, Sedatives)

- Lower ammonia level

- Lactulose aiming for 2-4 bowel movements daily → Rifaximin

- No need to follow blood ammonia levels or randomly check in asymptomatic patients

- Do not restrict protein: Maintain dietary protein intake of 1.2g to 1.5g/kg/day
Management of Gastroesophageal Varices

- GEV present in 50% cirrhotics: 30-40% compensated, 85% decompensated
- In compensated cirrhotics, varices develop at rate of 7-8%/year
- LS < 20kPA and platelet count > 150,000 very unlikely to have GE varices
- EGD to screen for gastroesophageal varices recommended with new diagnosis of cirrhosis
- If no varices on original EGD, repeat every 2 years with ongoing liver injury (obesity, alcohol) or 3 years (abstinence, viral elimination)
- Small varices (grade 1) on original EGD → repeat 1-2 years
- EGD at time of other clinical decompensation (ascites, encephalopathy)
- If cirrhosis but no varices → prevent clinical decompensation
- Grade 1 varices → Non-selective beta blocker
- Grade 2-3 varices → Non-selective beta blocker or variceal ligation

Hepatology 2017; 65: 310-332.
Management of Acute Bleeding in Cirrhotics

- Management of acute bleeding in cirrhotics depends on location, severity and degree of hemostatic impairment
- For variceal bleeding, major cause is increased portal pressure rather than bleeding diathesis
- For non-variceal bleeding, manage INR, platelet count and fibrinogen level:
  - Vitamin K (usually IV)
  - Transfuse platelet count to >50,000
  - Administer source of fibrinogen to get level ≥ 100-120mg/dL (Cryoprecipitate less volume than FFP)
  - Consider antifibrinolytic (Tranexamic or Aminocaproic acid)
- Thrombopoietin (TPO) receptor agonists not effective in acute bleeding
Management of Acute Variceal Hemorrhage

• Admit to ICU

• Upper endoscopy within 12 hours

• Restrictive blood volume resuscitation
  Initiating PRBC transfusion at hemoglobin of 7 g/dL and maintain hemoglobin at 7-9 g/dL

• Short-term antibiotic prophylaxis (maximum 7 days)
  IV Ceftriaxone 1g/24 hours is the antibiotic of choice

• Octreotide, Somatostatin, Terlipressin for 2-5 days → NSBB

• Consider TIPS in Childs C cirrhotics or Childs B with active bleeding

Transjugular Intrahepatic Portosystemic Shunt

- Hepatic Vein
- Portal Vein
- TIPS
- Splenic Vein
- Superior Mesenteric Vein
Management of Bleeding Gastric Varices

- Vasoactive drugs, restrictive transfusion, antibiotic prophylaxis
- Banding gastric varices can be technically difficult (IGV1 > GOV2 > GOV1)
- Cyanoacrylate glue injection
  - Polymerizes into firm clot within varix
  - Risk of distal embolization
  - Not approved by FDA for use in US, center dependent expertise
- TIPS
- Balloon-occluded retrograde obliteration (BRTO)
  - Balloon catheter in draining vessel (relies on spontaneous gastroscope shunt) then instill sclerosant/sponge
  - 90% long-term bleeding control
  - Can increase portal pressure: worsen esophageal varices, ascites
- EUS-guided transesophageal coiling of gastric varices
Optimal Timing of Referral for LT

Clinical Decompensation + Biochemical Decompensation (MELD >15)

- Encephalopathy
- Ascites
- Variceal Hemorrhage or chronic GI bleed from portal hypertensive gastropathy
- Hepatocellular Carcinoma
- Hepatorenal syndrome
- Hepatopulmonary syndrome or Portopulmonary Hypertension

Other considerations:
- Acute Liver Failure
- Poor quality of life or Recurrent, resistant infections in PSC/PLD
Timing: What is MELD?

- Model for End-stage Liver Disease
- Originally created to predict short term mortality post TIPS
- Basis for liver allocation in U.S. since 2/2002
- MELD-Sodium used since 1/2016
- 4 objective lab tests (Sodium, Total bilirubin, Creatinine, INR)
- Highly predictive of 3-month mortality in cirrhotics
- MELD of 15 is threshold patient survival with transplantation > survival without transplantation
Liver Disease Etiology of Adult Transplant Recipients

SRTR.transplant.hrsa.gov 2020
Exclusions for Liver Transplantation

MELD Score <15
Severe cardiac or pulmonary disease
AIDS
Ongoing alcohol or illicit substance abuse
HCC with metastatic spread
Uncontrolled sepsis
Anatomic abnormality that precludes liver transplant
Intrahepatic cholangiocarcinoma
Extrahepatic malignancy
Persistent non-compliance
Lack of adequate social support system

Hepatology 2014; 59: 1144-1165.
Living Donor Liver Transplantation

- ~5% of liver transplants in U.S. in 2020
- Patient must be listed for deceased donor transplant
- Anticipated prolonged time on wait list with MELD >15
- Recipients of LDLT are less sick: MELD 15-20
- Has family member or acquaintance with close relationship – no coercion
- In adult, take the right lobe (2/3 mass of liver) from donor → recipient
- Pediatric cases use left lobe living donor transplant
Liver Transplants in 2020 in 11 UNOS Regions

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<td>11</td>
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Summary

• Hepatic decompensation reduces survival
• MELD and CTP scores predict 3-month and 1-year mortality in hospitalized cirrhotics
• TIPS > LVP in management of refractory ascites
• Prevention of HRS includes antibiotics in UGI bleeding, IV albumin in SBP/LVP
• Nonselective beta blocker cessation in SBP
• Gastric varices: cyanoacrylate glue, TIPS, BRTO, EUS coiling in select patients
• Refer for liver transplantation: MELD ≥ 15 + clinical decompensation
A 61 year old HCV cirrhotic is admitted with abdominal pain and confusion. His admission creatinine is 2.1 (baseline 1.0), and he has evidence of SBP on tap (>250 PMNs). In addition starting Ceftriaxone, your next steps in management should include:

A) Stop Nadolol
B) Albumin infusion 1.5g/kg IV
C) Check urinalysis
D) Start Pentoxyfylline 300mg TID
E) A, B and C
A 61 year old HCV cirrhotic is admitted with abdominal pain and confusion. His admission creatinine is 2.1 (baseline 1.0), and he has evidence of SBP on tap (>250 PMNs). In addition starting Ceftriaxone, your next steps in management should include all except:

A) Stop Nadolol
B) Albumin infusion 1.5g/kg IV
C) Check urinalysis
D) Start Pentoxyfylline 300mg TID
E) A, B and C

The correct answer is E. This cirrhotic man has what appears to be acute kidney injury in the setting of spontaneous bacterial peritonitis (SBP). The urinalysis is recommended to evaluate the acute kidney injury, which could be hepatorenal syndrome (HRS) or something else. In SBP there is data to support cessation of non-selective beta blockers while the infection is being treated, as well as giving albumin infusion of 1.5 mg/kg of body weight to prevent HRS on the first day of treatment. There is no data to support the use of Pentoxyfylline in cirrhotics with acute kidney injury or SBP.
On hospital day #2, this patient has massive hematemesis. Urgent endoscopy shows grade III esophageal varices with red wale signs. He has 3 bands placed. Next steps should include:

A) Octreotide IV for 72 hours  
B) Consider BRTO before he rebleeds 
C) Transfuse to keep hemoglobin > 10g/dL 
D) Referral for urgent liver transplantation
On hospital day #2, this patient has massive hematemesis. Urgent endoscopy shows grade III esophageal varices with red wale signs. He has 3 bands placed. Next steps should include:

A) Octreotide IV for 72 hours  
B) Consider BRTO before he rebleeds  
C) Transfuse to keep hemoglobin > 10g/dL  
D) Referral for urgent liver transplantation

The correct answer is A. Management of an acute esophageal variceal bleeding includes upper endoscopy within 12 hours, vasoactive medications such as Octreotide for 72 hours and antibiotic prophylaxis. A hemoglobin threshold of > 7g/dL reduces the risk of rebleeding when compared to a transfusion threshold of > 9g/dL. BRTO is used in management of isolated gastric variceal bleeding. Acute variceal bleeding is not an indication for urgent liver transplantation, and it does not give additional points to the MELD score.
Select References

• N Terrault et al. Avatrombopag Before Procedures Reduces Need for Platelet Transfusion in Patients with Chronic Liver Disease and Thrombocytopenia. Gastroenterology 2018; 155: 705-718.