Management of Hospitalized Patients with Cirrhosis

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Disclosure

Research Support: Gilead, Genfit, Conatus and Intercept

Advisory: Gilead
Outline

- Complications of cirrhosis
  1. Portal hypertension related variceal bleed
  2. Ascites, hyponatremia and hydrothorax
  3. Hepatic encephalopathy
  4. Renal failure and HRS

- Infections in cirrhosis
- Liver transplantation

Natural History of Cirrhosis

Compensated cirrhosis → Decompensated cirrhosis → Death

Development of complications:
- Variceal hemorrhage
- Ascites
- Encephalopathy
- Jaundice
Question

- Most common decompensation in patient with cirrhosis?

1. Variceal bleed.
2. Hepatic encephalopathy.
3. Ascites.
4. HCC.
5. Jaundice.

Complications in Compensated Cirrhosis

Decompensation Shortens Survival

Median survival ~ 9 years

Median survival ~ 1.6 years


Cirrhosis Nomenclature

Compensated
- No PHTN
- Mild PHTN (HVPG > 5 < 10mmHg)
- Clinically Significant Portal Hypertension (CSPH)
  HVPG ≥ 10mmHg

Decompensated
- Ascites
- Encephalopathy
- Variceal bleed

Further decompensated
- Recurrent variceal bleed
- Refractory ascites
- Hepatorenal syndrome
- Recurrent HE
Varices and Portal Hypertension related Bleeding

- Seen in 50% patients with cirrhosis
- 10-15% of all GI bleeds (~ 40,000 patients)

Esophageal Varices

- Seen in 50% patients with cirrhosis
- 10-15% of all GI bleeds (~ 40,000 patients)
Large Varices Are More Likely To Rupture

2-year probability of first bleed:
- Small varices: 7%
- Large varices: 30%

Better Bleeding Control Resulted in Decrease Mortality

- Pharmacotherapy
- Endoscopic innovations
- IR Procedures
- Better ICU care

- Protect the liver
- Protect the kidney
- Prevent infections
Case Presentation

- 60-year-old female with NASH cirrhosis is brought to the ER because of melena. No prior endoscopy. Hgb is 8 (baseline 11).
- What is the best pharmacologic treatment option to start?

1. IV PPI.
2. IV PPI and IV octreotide.
3. PO PPI, octreotide and antibiotics.
4. IV PPI, octreotide and antibiotics.

Case Presentation

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1. IV PPI.
2. IV PPI and IV octreotide.
3. PO PPI, octreotide and antibiotics.
4. IV PPI, octreotide and antibiotics.
Case Presentation

- 50-year-old male with HCV related cirrhosis is brought to the ER because of melena and hypotension (SBP 80 mmHg). What is the first priority in the management of this patient?

- Emergent upper endoscopy.
- Start antibiotics for SBP prophylaxis.
- Transfuse blood.
- Venous access and hemodynamic stability.
Initial Management of Variceal Bleed

- Intubate and send to ICU
- Place 18 Gauge IVs x 2
- Bolus PPI and start drip
- Corrected coagulopathy (I like fibrinogen > 100, plts > 50K, INR < 2)
- Blood transfusion parameters?
- Antibiotics?
- Splanchnic vasoconstrictor?

Transfusion Strategy: More Isn’t Better

- RCT of n=921 pts with UGIB
- Transfused to Hg <7 vs liberal transfusion Hg <9.

- Restrictive strategy → NO increase in portal pressure

- Liberal transfusion strategy → increased portal pressure and twice as much rebleeding (11% vs 22%)

- Survival was improved with restrictive transfusions

Villanueva et al, NEJM 2013
Prophylactic Antibiotics Reduce Recurrent Variceal Hemorrhage

Prophylactic antibiotics (n=59) vs No antibiotics (n=61)

Greatest benefit in first 7 days

Follow-up (months)

% free of variceal hemorrhage

Hou et al., Hepatology, 2004

Prophylactic Antibiotics Decrease Rebleeding Risk and Improve Survival

No antibiotics

Antibiotics

Infection

Death

Rebleeding

Bernard et al., Hepatology 1999

Hou M-C et al., Hepatology 2004

* p<0.05
### Which Antibiotic?

**AASLD Guidelines:**

- Oral norfloxacin or IV ciprofloxacin x 7d
- IV ceftriaxone may be preferred in advanced cirrhosis if high prevalence of quinolone resistance
- **Personal Practice: Ceftriaxone**

### Splanchnic Vasoconstriction

**Vasopressin:**
- Most potent splanchnic vasoconstrictor
- Extensive SE (myocardial, mesenteric ischemia)
- Max use 24 hrs

**Terlipressin:**
- Synthetic vasopressin analogue
- Longer acting, lower SE
- Not available in US

**Somatostatin & Analogues:**
- **Octreotide**, vapreotide, somastostatin
- Splanchnic vasoconstriction
- Fewer SE than vasopressin
- Only octreotide available in US
- Treat for 3-5 days

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Endoscopic Band Ligation

Refractory Variceal Bleeding

- Balloon tamponade
- TIPS
- Surgical shunt
1. Second rebleed for esophageal varices
2. First bleed for gastric varices
3. Rebleed on combination endoscopic plus pharmacologic therapy (10-20%)

**Transjugular Intrahepatic Portosystemic Shunt**

- Hepatic vein
- TIPS
- Portal vein
- Splenic vein
- Superior mesenteric vein

**Portal Hypertensive Bleed**

- Gastric Varices Treatment
  - Glue
  - TIPS
- Portal HTN Gastropathy Treatment
  - NSBB
  - Iron
  - TIPS (if severe)
- GAVE (watermelon stomach) Treatment
  - APC (argon plasma)
  - Iron
Case

- 56 yr with acute variceal bleed (1st episode)
- Bleeding controlled with band ligation
- No bleeding for 5 days
- MAP 90 mmHg

Which is the best discharge regimen?

1) Beta blockers and nitrates
2) Serial ligation alone
3) Ligation and beta blockers
4) TIPS
5) Portacaval shunt
Lowest Rebleeding Rates are Obtained in HVPG Responders and With Ligation + β-Blockers

Statins Improve Survival After EV Bleed

- RCT of patients with recent EV bleed: EBL+ BB + placebo vs EBL + BB + statin
- 2010-2013, n=158 patients, groups stratified by CTP score
- Simvastin 20mg daily started 5-10 post bleed, escalated to 40mg daily by day 15
- Patients followed to 24 months

*Bosch and García-Pagán, Lancet 2003; 361:952

* ↓ HVPG <12 mmHg or >20% from baseline

Abraldes et al. Gastro, 2016
Statins and Rebleeding Risk


Statins Improve Survival After Variceal Bleed

Abraldes et al. Gastro, 2016
Statins Decrease Risk of Decompensation and Death

- Retrospective, VA study of 40K men
- From 1996-2009, all men with compensated HCV cirrhosis
- Statins were associated with decreased risk:
  - Decompensation: HR 0.55; 95% CI, 0.39-0.78
  - Mortality: HR 0.55; 95% CI 0.45-0.68
  
  (Adjusted for age, FIB-4, serum albumin, MELD and CTP)

Mohanty et al, Gastroenterology, Feb 2016

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Statins effects in portal hypertension?

- Improve endothelial dysfunction
- Decrease intrahepatic vascular tone
- Improve hepatic blood flow and liver function
  + Antifibrotic Properties!

MORE TO COME ON BENEFITS OF STATINS IN PORTAL HYPERTENSION!
Acute Variceal Bleed
Key Points

Suspected variceal bleeding
Octreotide
Antibiotics (i.v. ciprofloxacin or ceftriaxone), volume restitution
Endoscopy (Diagnostic + therapeutic)

Control
Octreotide 2-5 days
Initiate secondary prophylaxis

Failure
Balloon tamponade if required
TIPS

Ascites
Causes of Ascites

<table>
<thead>
<tr>
<th>Cause</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis</td>
<td>80%</td>
</tr>
<tr>
<td>Malignancy</td>
<td>10%</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>4%</td>
</tr>
<tr>
<td>Nephrotic Syndrome</td>
<td>2%</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>2%</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>1%</td>
</tr>
<tr>
<td>Others (Budd Chiari)</td>
<td>1%</td>
</tr>
</tbody>
</table>

Case

- 47 yr old male with hepatitis C cirrhosis now presented with new onset abdominal distention and leg swelling.
- Ultrasound showed large ascites.

INR 2.2
Which Statement is correct?

1. Need correction of INR before paracentesis.
2. No need to send cell count as no abdominal pain and fever.
3. SAAG of > 1.1 is only seen in portal hypertension.
4. Direct inoculation into blood culture bottles at the bedside improves yield.

Which Statement is correct?

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2. No need to send cell count as no abdominal pain and fever.
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4. Direct inoculation into blood culture bottles at the bedside improves yield.
SAAG

- Serum-ascites albumin gradient
  - SAAG = serum albumin – ascites albumin
  - SAAG ≥1.1 g/dL is 97% accurate at diagnosing ascites due to portal hypertension
  - High SAAG and high total protein (>2.5 g/dL) suggests cardiac cause

Probability of Survival is Poor After Developing Ascites

56%
5 year survival

When to Perform Paracentesis

- Rule out SBP
- Any new onset ascites
- Any admission to hospital
- Worsening of controlled ascites
- Any change in clinical status
  -- Encephalopathy
  -- Unexplained renal failure

Ascitic Fluid Analysis

<table>
<thead>
<tr>
<th>Routine</th>
<th>Optional (Suspicion for Infection)</th>
<th>Unusual</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell count &amp; differential</td>
<td>Culture (bedside)</td>
<td>AFB</td>
</tr>
<tr>
<td>Albumin</td>
<td>Glucose</td>
<td>Bilirubin</td>
</tr>
<tr>
<td>Total Protein</td>
<td>LDH</td>
<td>Triglyceride</td>
</tr>
<tr>
<td></td>
<td>Amylase</td>
<td>Cytology</td>
</tr>
<tr>
<td></td>
<td>Gram stain</td>
<td></td>
</tr>
</tbody>
</table>

*Runyon, Hepatology 2004*
Management of Ascites

First-Line Therapy

Tense ascites
Paracentesis
Sodium restriction (<2 Gm/24 Hrs) and diuretics*

Non-tense ascites

Second-Line Therapy

Refractory Ascites 10 %

- Repeated large volume paracentesis†
- TIPS
- Liver Transplantation

*Diuretics: Spironolactone 100 mg/day, furosemide 40 mg/day or bumetanide 1 mg/day, uptitrate stepwise to spironolactone 400 mg/day, furosemide 160 mg/day or bumetanide 4 mg/day as tolerated

Adapted from Runyon BA. Hepatology. 2009.

Treatment of Refractory Ascites

Large volume paracentesis
Transjugular Intra-hepatic Porto-systemic Shunt
TIPS vs. Serial Paracentesis

TIPS LVP
Encephalopathy
Total 15% 28%
GI bleeding 8% 13%
SBP 2% 3%
HRS 5% 13%

Portal hypertensive complications

Table:

<table>
<thead>
<tr>
<th></th>
<th>TIPS</th>
<th>LVP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>15%</td>
<td>28%</td>
</tr>
<tr>
<td>GI bleeding</td>
<td>8%</td>
<td>13%</td>
</tr>
<tr>
<td>SBP</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>HRS</td>
<td>5%</td>
<td>13%</td>
</tr>
</tbody>
</table>


Albumin for LVP

- Patients receiving albumin had less hemodynamic deterioration, renal failure and hyponatremia
- 6-8 gm albumin per L of ascites removed if >5 L removed
- Recent meta-analysis of 17 studies have shown improved survival in the albumin group

Table:

<table>
<thead>
<tr>
<th>Paracentesis Volume</th>
<th>Albumin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4.0 L</td>
<td>0</td>
</tr>
<tr>
<td>4.1-5.0 L</td>
<td>12.5 gm (25% 50mL)</td>
</tr>
<tr>
<td>5.1-6.0 L</td>
<td>25.0 gm (25% 100mL)</td>
</tr>
<tr>
<td>6.1-8.0 L</td>
<td>37.5 gm (25% 150mL)</td>
</tr>
<tr>
<td>&gt;8.1 L</td>
<td>50 gm (25% 200mL)</td>
</tr>
</tbody>
</table>

Gines et al, Gastro 1988
Post-Paracentesis Circulatory Dysfuntion (PCD) Depends on the Type of Plasma Volume Expander and the Amount of Ascites Removed


LVP Without Albumin Leads to Increases in Renin, Renal Failure and Hyponatremia

Gines et al., Gastroenterology 1988; 94:1493
Risk of Bleeding after Paracentesis

- 1,100 outpatient therapeutic paracentesis (median 8.7 L)
  - Median platelet count 50,400 (19,000-341,000), mean INR 1.7 (0.9-8.7)
  - No bleeding episodes
  - Risk of bleeding is due to collateral veins in the peritoneum

Routine Prophylactic Use of Fresh Frozen Plasma or Platelets before Paracentesis?

- Not recommended
- Complications were reported in only about 1% of patients
- Bleeding conditions occur in less than 1 per 1,000
- Risk of bleeding if coagulopathy with DIC or hyperfibrinolysis

Ascitic Fluid Analysis: Cell Count

- Normal ascites
  - Total WBC upper limit 500 cells/mm³
  - PMNs normally account for 25-30%

- SBP definition PMNs >250 cells/mm³
- Culture: Direct inoculation into blood culture bottles at the bedside to improve yield (50%→80%)

SBP

- Start broad spectrum antibiotics immediately
- IV albumin (1 g/kg on day#1 & 1.5 g/kg on day #3)

- Community acquired SBP
  - Causes: Gram negative (*E. Coli*)
  - 3rd generation cephalosporin (cefotaxime for 5-7 days)

- Hospital acquired SBP
  - High risk of ESBL *E.coli*

- Treatment Failure
  - Secondary bacterial peritonitis
  - Resistant organism
## Treatment Trials for SBP

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Results</th>
<th>p</th>
<th>Hospital Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefotaxime 5 vs 10 days</td>
<td>100</td>
<td>Cure 93% vs 91% Recurrence 12% vs 13%</td>
<td>NS</td>
<td>33% vs 43%</td>
</tr>
<tr>
<td>Oral ofloxacin vs cefotaxime</td>
<td>123</td>
<td>Resolution 84% vs 85%</td>
<td>NS</td>
<td>19% vs 19%</td>
</tr>
<tr>
<td>Cefotaxime with or without Albumin</td>
<td>126</td>
<td>Resolution 98% vs 94%</td>
<td>NS</td>
<td>10% vs 29%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal failure 10 vs 33%</td>
<td>0.002</td>
<td></td>
</tr>
</tbody>
</table>

### Recurrence of SBP is Common so Need for Secondary Prophylaxis

The probability of SBP recurrence over time is shown in the graph below:

- **Probability of SBP recurrence** vs **Months**
- **Graph Source:** Titó et al., Hepatology 1988; 8:27
- **70%** probability at 36 months
Case

- 47 yr old male with hepatitis C cirrhosis with ascites. He is on lasix and aldactone which was recently increased.
- Exam showed large ascites.
- Now fatigue and worsening encephalopathy.

Which statement is NOT True

- Need to stop diuretics.
- Start hypertonic saline.
- Fluid restriction.
- Associated with increase mortality.
Which statement is NOT True

- Need to stop diuretics.
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Potential Consequences of Hyponatremia

- Hepatic encephalopathy
- Reduced quality of life
- Increased risk of hepatorenal syndrome and death
- Neurologic consequences after liver transplantation
  - Central Pontine Myelinolysis
    - Associated with rapid correction of sodium
    - May not be reversible
# Types of Hyponatremia in Cirrhosis

<table>
<thead>
<tr>
<th></th>
<th>Hypovolemic Hyponatremia</th>
<th>Hypervolemic Hyponatremia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
<td>Na&lt;130 in setting of intense sodium loss and contraction of intravascular volume</td>
<td>Na&lt;130 in setting of solute free water retention and expansion of ECF volume</td>
</tr>
</tbody>
</table>
| **Clinical Findings** | Develops in a few days
Signs of dehydration
No ascites/edema
Encephalopathy present | May be transient
Ascites/edema present
Encephalopathy variable |
| **Causes**       | Over diuresis
Sodium loss
Diarrhea                                                                 | Excess of solute-free water
(spontaneous, fluid induced, drug induced, infections) |
| **Management**   | Stop diuretics
Treat diarrhea
IV albumin
Give sodium cautiously | Reduce fluid intake: free water restriction
Increase free-water excretion |
Conclusions

- Ascites is very common in cirrhosis
  - Should be tapped whenever new, different, or admitted to the hospital
- Low index of suspicion for SBP
- Need IV albumin for LVP
- Hyponatremia should be managed according to overall volume status of the patient

Case

- 47 yr old male with NASH cirrhosis. History of hepatic hydrothorax. Now with worsening SOB.
- He had 2 thoracentesis last month. Meld score 20.

Best long term treatment for him?
1. Chest tube placement
2. Pleurodesis
3. TIPS procedure
4. Liver transplant
Case

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Hepatic Hydrothorax

- Occurs in 5-10% with decompensated cirrhosis
- Passage of ascites through diaphragmatic defect
- Risk of spontaneous bacterial pleuritis
- Mainstay is control of ascites
- Chest tube is not indicated
Hepatic Hydrothorax:
Treatment Options

- Repeated thoracentesis
- TIPS (50% patient may not be candidate)
- VATS and diaphragmatic repair (low success rate and high mortality)
- Denver shunt (pleuro-venous shunt)
- PleurX Catheter
- Liver Transplantation

Hepatic Encephalopathy
Case

- 47 yr old male with hepatitis C cirrhosis. Wife brought him to ER with 3rd episode of hepatic encephalopathy.
- On exam he is sleepy and has asterixis.
- What is not needed in the work up?

1. Infectious work up.
2. Rectal exam/melena.
3. Diagnostic paracentesis.
4. Ammonia level.

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1. Infectious work up.
2. Rectal exam/melena.
3. **Diagnostic paracentesis.**
4. Ammonia level.
Impact of Hepatic Encephalopathy

- 111,000 hospitalizations per year
- Average length of stay for hospitalization with HE is 8.5 days
- Total $ for hospitalizations with HE estimated to be $7.254 billion nationwide (2009)


Prevalence Hepatic Encephalopathy

- Two forms of HE are recognized: Overt and Minimal based on the nature and severity of clinical manifestations
- Overt hepatic encephalopathy (OHE) occurs in:
  - 30 to 45% of cirrhotic patients
  - 10 to 50% of patients with TIPS

Poordad FF. Aliment Pharmacol Ther 2006.
Blood Ammonia and Diagnosis of HE

- **Accuracy is Technique-Dependant**
  - Efficient venous draw, rapid transport on ice to reliable lab, quick analysis, pH controlled
- **Not Specific**
  - Elevated in TPN, GI hemorrhage, intense muscular activity, and urosepsis
- **Limited Reliability**
  - Overt HE is not always accompanied by a very high ammonia
- **Not a Guide to Treatment**
  - Not a useful clinical endpoint for HE treatment in practice

Case

- A 63-year-old woman with NASH cirrhosis in the ER.
- She had slurring of her speech and was “confused,” according to her husband that worsened overnight
- It was difficult for her to maintain her balance and fell while in the bathroom and hit her head

- First step in management is?
  1. Blood cultures.
  2. Ultrasound.
  3. Head CT.
  4. Diagnostic paracentesis.
Case

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Precipitating Factors Involved in Overt HE

- Infection
- Shock
- Anemia
- Surgery
- GI hemorrhage
- Constipation
- Portosystemic shunt
- Deterioration in liver function
- Renal/electrolyte disturbances:
  - Renal failure
  - Metabolic alkalosis
  - Hypovolemia
  - Hypokalemia
  - Hyponatremia
- Psychoactive Medications
  - Benzodiazepines
  - Narcotics, sedatives
- Dietary protein Noncompliance

HE Treatment Goals

1. Provide supportive care
2. Identify and remove precipitating factors
3. Reduce nitrogenous load from gut
4. Assess need for long-term therapy


Treatment Options for OHE

- Reduction of nitrogenous load from gut
  - Bowel cleansing (PEG)
  - Non-absorbable disaccharides (lactulose)
  - Antibiotics (rifaximin, metronidazole)*
  - Agents that bind NH₃ in the gut
    - Na benzoate
    - Na phenylacetate
    - Na hydroxybutyrate
    - Glycerol phenyl butyrate

- Drugs that affect neurotransmission (flumazenil, bromocriptine)

- Manipulation of splanchnic circulation (occlusion of portal-systemic collaterals)
  - Occlude TIPS shunt if present

- Probiotics
- Zinc

* Neomycin (historical interest).

Lactulose

- Mechanism of action:
  - A non-absorbable disaccharide
  - Bacterial flora metabolizes in the colon to lactic acid lowers the colonic pH

- Administered orally, by mouth or through a nasogastric tube or via retention enemas
- Start 25 mL every 1-2 hours until bowel movements
- Monitor stool output and side effects

Ferenci P. Semin Liver Dis. 2007.
Bajaj JS. Aliment Pharmacol Ther 2010.

Rifaximin

- Minimally absorbed (<0.4%) oral antibiotic
- No dosing adjustment required in patients with liver disease or renal insufficiency
- Approved for overt recurrent HE risk reduction (58% ↓ in risk of HE breakthrough)

A Randomized, Double-Blind, Controlled Trial Comparing Rifaximin Plus Lactulose With Lactulose Alone in Treatment of Overt Hepatic Encephalopathy

Am J Gastroenterol 2013 Sep;108(9)

- 48 (76 %) in lac/rif gp compared with 29 (50.8 %) in lactulose gp had complete reversal of HE ($P < 0.004$)

- There was a significant decrease in mortality after treatment with lac/rifaximin vs. lactulose (23.8 % vs. 49.1 %, $P < 0.05$)

- Patients in the lac/rif gp had shorter hospital stay (5.8 vs. 8.2 days, $P = 0.001$)
13/25 patients in the standard therapy arm (52%) had an improvement of 1 or more in HESA score as compared with 21 of 23 patients receiving PEG (91%) (P < .01)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N = 50)</th>
<th>Lactulose (n = 25)</th>
<th>PEG (n = 25)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-h HESA score change, mean (SD)</td>
<td>1.1 (0.8)</td>
<td>0.7 (0.8)</td>
<td>1.5 (0.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>Length of stay, d</td>
<td>6 (9)</td>
<td>8 (12)</td>
<td>4 (3)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Covert Hepatic Encephalopathy

- Significantly diminishes quality of life
- Significantly diminishes working and earning capacity in blue-collar workers
- Increased progression to Overt HE
- Impairs driving on structured driving tests
- Increases risk of traffic accidents and violations

Legal Obligation regarding driving in HE

- Only 6 states (CA, OR, NV, PA, DE and NJ) require providers to report medically impaired drivers but HE is not mentioned specifically in any state

- We do recommend patients with Overt HE against driving

HE Summary

- HE is very common in the cirrhotic patient
- Ammonia is not useful for clinical endpoint in HE treatment
- Look for precipitating factors of HE
- Minimize narcotics and sedatives
- Lactulose and rifaximin are the main treatment options
Renal Dysfunction in Cirrhosis

The Kidneys are also important?

- Renal dysfunction is one of the most important risk factors for adverse outcomes in patients with cirrhosis
- Found in 20% of cirrhotic’s admitted to the hospital
- Acute kidney injury (AKI) in cirrhosis is associated with:
  - 7-fold increase in overall mortality

Case

- 50 yr old female with hepatitis C cirrhosis complicated by ascites. He is on diuretics.
- No new medications. Normal creatinine last week.

Case

- What is the most likely etiology his AKI?

1. Hepatorenal syndrome (HRS).
2. Obstructive (post-renal).
3. Pre-renal azotemia.
4. ATN.
5. Cryoglobulinemia.
Case

- What is the most likely etiology his AKI?

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3. Pre-renal azotemia.
4. ATN.
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Differential Diagnosis of Renal Dysfunction in Cirrhotics

- Pre-renal azotemia
  - Hepatorenal syndrome
- Intrinsic renal disease
- Post-renal disease
Intrinsic Renal Disease

<table>
<thead>
<tr>
<th>Type</th>
<th>Typical clinical setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute tubular necrosis (ATN)</td>
<td>Hypotension, IV contrast, prolonged hepatorenal syndrome</td>
</tr>
<tr>
<td>Acute interstitial nephritis (AIN)</td>
<td>Beta-lactam antibiotics (Zosyn, Augmentin), cephalosporins (ceftriaxone), NSAIDs</td>
</tr>
<tr>
<td>IgA nephropathy*</td>
<td>Cirrhosis, especially alcoholic</td>
</tr>
<tr>
<td>Membranous nephropathy*</td>
<td>Hepatitis B / C</td>
</tr>
<tr>
<td>Membranoproliferative glomerulonephritis (MPGN) / cryoglobulinemia*</td>
<td>Hepatitis B / C</td>
</tr>
</tbody>
</table>

* Renal biopsy is needed to make the diagnosis.

Pre-Renal Azotemia

- The most common cause of AKI in cirrhosis
- Diagnostic evaluation:
  - Urine studies (fractional excretion of sodium)
  - R/o obstruction
- Management:
  - IV hydration with IV albumin 1g/kg
  - Treat the underlying cause
  - Remove the offending agent
Hepatorenal syndrome (HRS)

- Functional pre-renal azotemia
- 85% have an identifying stressor

<table>
<thead>
<tr>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid (&lt;2 weeks)</td>
<td>Speed</td>
</tr>
<tr>
<td>2x baseline and &gt;2.5 mg/dL</td>
<td>Creatinine &gt;1.5 mg/dL</td>
</tr>
<tr>
<td>Typically SBP</td>
<td>Associated with Refractory ascites</td>
</tr>
<tr>
<td>Reversible</td>
<td>Response to treatment May be reversible but usually recurs</td>
</tr>
<tr>
<td>Extremely poor (days-weeks)</td>
<td>Prognosis Poor (months)</td>
</tr>
</tbody>
</table>


Diagnostic Criteria of Hepatorenal Syndrome

- Presence of cirrhosis with ascites
- Serum creatinine >1.5 mg/dL
- No improvement in creatinine after:
  - Withdrawal of diuretics, and
  - 1 g/kg IV albumin per day (up to 100g/day max) for 2 days
- Absence of circulatory shock
- No recent administration of nephrotoxic medications
- Absence of intrinsic renal disease
  - Normal renal ultrasound
  - Bland urinalysis (no blood; <0.5 g/day protein)

International Ascites Club Guidelines.
Management of Hepatorenal Syndrome

**STEP 1**
- IV Albumin 1g/kg per day x 2 days (max 100g/day)
- Treat precipitating factors

**STEP 2**
- **Start vasoconstrictors**
  - Midodrine 7.5 mg PO TID
  - Octreotide 100 mcg SQ TID
  - Continue IV albumin 25-50 g/day

**STEP 3**
- **Titrate**
  - Raise mean arterial pressure (MAP) by >15 mmHg
  - Max midodrine 15 mg TID, octreotide 200 mcg TID

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An Open Label, Pilot, Randomized Controlled Trial of Noradrenaline Versus Terlipressin in the Treatment of Type 1 Hepatorenal Syndrome and Predictors of Response


*Am J Gastroenterol* 2008 Jul;103(7):1689-97

- 40 patients with HRS-1 randomized to noradrenaline 0.5–3.0 mg/h + albumin (N = 20) or terlipressin 0.5–2 mg + albumin (N = 20), until reversal of HRS (primary end point) or completion of 15 days of therapy (secondary end point)

- At similar time points, 10 (50%) patients in each group achieved primary end points

---

![Graphs showing results of the trial](image-url)
Key Points

- Acute kidney injury is an important prognostic marker in cirrhotics
  - 50% risk of death in the first month
- Causes can be categorized as:
  - Pre-renal (most common)
  - Intrinsic renal
  - Post-renal
- Hepatorenal syndrome is diagnosed after an IV albumin challenge and ruling out other causes of AKI
  - Managed with midodrine, octreotide, and albumin

Could Beta Blockers Be Harmful in Cirrhosis?
Window Period of Safe BB Use

- Beta-blockers are not indicated in early cirrhosis, may increase adverse events
- Beta-blockers may be indicated for cardiovascular indications

Window opens
- Beta-blockers are indicated for primary prophylaxis of variceal bleeding
- Beta-blockers are indicated for secondary prophylaxis of variceal bleeding

Window closes
- Beta-blockers are contraindicated under the following situations:
  - Refractory ascites
  - Systolic blood pressure < 100mm Hg
  - Mean arterial pressure < 60mm Hg
  - Acute kidney injury
  - Hepatorenal syndrome
  - Spontaneous bacterial peritonitis
  - Sepsis
  - Poor medical follow-up
  - Patient noncompliance

Window does not re-open

Infections in Cirrhosis

- Bacterial infections are the leading cause of mortality in cirrhosis
- One third patients have at least one infection
- Increase in MDR organisms (40% in some latest studies)

### Bacterial Infections in Cirrhosis

<table>
<thead>
<tr>
<th>Site</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>30 %</td>
</tr>
<tr>
<td>UTI</td>
<td>25 %</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>20 %</td>
</tr>
<tr>
<td>Soft Tissue infection</td>
<td>10 %</td>
</tr>
<tr>
<td>Sepsis</td>
<td>5 %</td>
</tr>
<tr>
<td>Other</td>
<td>10 %</td>
</tr>
</tbody>
</table>

### Septic Shock in cirrhotic patients
- Retrospective, 635 cirrhotics with sepsis
- Mortality 75%
- Fungal infections seen in 10% patients
- Septic shock but Culture negative: 25%

*Arabi YM et al. Hepatology 2012*
Does Timing and choice of antibiotics makes a difference?

- Inappropriate initial empiric antimicrobial therapy was administered in 25%.
- The median time to appropriate antimicrobial was 7.3 hours.
- In bacterial septic shock, a single rather than 2 or more appropriate antimicrobials was used in 73%.

Arabi YM et al. Hepatology 2012

Timing of Antibiotics by onset of hypotension and mortality

Arabi YM et al. Hepatology 2012
Key Points

- Sepsis mortality is high in cirrhosis about 60-80%
- Bacterial infections are the most common infections
- Low threshold for starting the antibiotics
- Increase in resistant organisms

Liver Transplantation
Liver Transplantation
Timing of Referral

- Early referral is the key
- Complications of Cirrhosis (Child’s B or C)
  - Ascites
  - Portal hypertensive bleeding
  - Hepatic encephalopathy
  - Spontaneous bacterial peritonitis
  - Synthetic function abnormalities
- Waiting list priority is based on liver disease severity (=MELD), not waiting time

Deceased Donor Liver Allocation
February 2002 Changes:

Child-Turcotte-Pugh Score ➔ MELD Score
- Ascites ➔ Creatinine
- Encephalopathy ➔ Bilirubin
- Bilirubin ➔ Protime INR
- Protime INR ➔ Albumin

MELD Score = 0.957 x Log_e (creatinine mg/dL) + 0.378 x Log_e (bilirubin mg/dL) + 1.120 x Log_e (INR) + 0.643
MELD Score Predicts 90 Day Mortality

90 day % risk of death

MELDNa: Incorporating Na to MELD

MELDNa = MELD - Na - 0.025*MELD*(140-Na) + 140

Kim NEJM 2008;1018
Key Points

- Avoid narcotics, sedatives and NSAID’s
- Tylenol is safe (max dose 2 grams per day)
- Avoid IV fluids (NS), use IV albumin
- Low threshold of starting antibiotics
- Any change in clinical status need infectious work up and paracentesis
- Please monitor stool output on lactulose
- Early referral to transplant center

THANK YOU

"Is life worth living? It all depends on the liver.”
William James, American philosopher (1842)