Care of the Hospitalized Cirrhotic Patient

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Questions to Answer

- How should I interpret ascites fluid and manage albumin therapy with paracentesis?
- What are paracentesis complications?
- Are there strategies for the malnourished cirrhotic patient?
- How can I best assess hepatic encephalopathy?
- Is there a safe role for pain medications in cirrhosis?
Ascites – AASLD guidelines

- Paracentesis is part of the physical exam in a patient with ascites (high suspicion for SBP)
- Ascites not always liver related (cardiac, renal failure, peritoneal disease)
- Useful tests for ascites fluid
  - Initial Presentation – albumin & protein
  - Every Presentation - cell count with differential

Table 3. Ascitic Fluid Laboratory Data*

<table>
<thead>
<tr>
<th>Routine</th>
<th>Optional</th>
<th>Unusual</th>
<th>Unhelpful</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell count and differential</td>
<td>Culture in blood culture bottles</td>
<td>AFB smear and culture</td>
<td>pH</td>
</tr>
<tr>
<td>Albumin</td>
<td>Glucose</td>
<td>Cytology</td>
<td>Lactate</td>
</tr>
<tr>
<td>Total protein</td>
<td>Lactate dehydrogenase</td>
<td>Triglyceride</td>
<td>Cholesterol</td>
</tr>
<tr>
<td></td>
<td>Amylase</td>
<td>Bilirubin</td>
<td>Fibronectin</td>
</tr>
<tr>
<td></td>
<td>Gram’s stain</td>
<td></td>
<td>Glycosaminoglycans</td>
</tr>
</tbody>
</table>

Abbreviation: AFB, acid-fast bacteria. *Adapted from Runyon. Reprinted with permission from W.B. Saunders.
The International Ascites Club was founded in Florence, Italy on November 30, 1990 during an international liver meeting organized by Professor Paolo Gentilini. The reason to found a club of experts in this complication of portal hypertension originated from the peculiarity of the expertise doctors who treat patients with ascites must have.
Ascites

- SAAG = serum-ascites albumin gradient
  - Calculation: serum albumin – fluid albumin
    - SAAG ≥ 1.1 = portal HTN
- Fluid Protein < 2.5 mg/dL – suggestive of underlying liver disease or dysfunction
- Spontaneous Bacterial Peritonitis (SBP)
  - Cell count – Fluid neutrophils ≥ 250 cells/mL
  - Antibiotics – Ceftriaxone or Cefotaxime
  - “Don’t forget the albumin”
Case #1 – How much albumin??

- 56M with alcoholic cirrhosis
- Abdominal distention, known history of ascites
- Wt – 70kg, Afebrile, non toxic appearing
- Paracentesis completed – 6 liters removed
- WBC – 1000 (Seg – 60%)
This patient has SBP?

A. True

B. False
How much albumin does this patient need?

A. 25 grams  
B. 50 grams  
C. 100 grams
Results

A. 25 grams
B. 50 grams
C. 100 grams
Albumin Replacement

- Large Volume Paracentesis
  - 7-8 gm of albumin for every Liter removed
  - Standard of care/indicated when LVP ≥ 5 Liters

- Spontaneous Bacterial Peritonitis
  - Day 1 - 1.5gm/kg
  - Day 3 - 1gm/kg
  - Clearly reduces renal failure and mortality
    - NNT (renal failure) = 4
    - NNT (mortality) = 5
Complications of Paracentesis

- Rare short term complications
  - Hemorrhage
  - Intestinal Perforation
Z tracking and Paracentesis Location

Not as effective as advertised

Best Location for Para?

A

Cecum

B

X

C

A
Prospective Study on Complications

- 2005 - 2007 - France and Switzerland
- 515 paracentesis in 171 patients
- Ultrasound available for all - only used 11.7%

- 54 complications (10.5%)
  - Minor - self-limited - 46 cases (8.9%)
  - Major - medical intervention - 8 cases (1.6%)

De Gottardi, et al., Clinical Gastro Hepatology, 2009 (7), 906-909
### Prospective Study on Complications

<table>
<thead>
<tr>
<th>Procedure with Complications</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>no complications</td>
<td>461 (89.5%)</td>
</tr>
<tr>
<td>minor complications</td>
<td>46 (8.9%)</td>
</tr>
<tr>
<td>major complications(^b)</td>
<td>8 (1.6%)</td>
</tr>
<tr>
<td>Small bowel perforation(^b)</td>
<td>2 (0.4%)</td>
</tr>
<tr>
<td>Iatrogenic percutaneous infection of ascites(^b)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Ascites outflow at the puncture site after the procedure</td>
<td>26 (5.0%)</td>
</tr>
<tr>
<td>Self-limited</td>
<td>15 (2.9%)</td>
</tr>
<tr>
<td>Necessitating a stoma pouch</td>
<td>11 (2.1%)</td>
</tr>
<tr>
<td>Bleeding after the procedure</td>
<td>17 (3.3%)</td>
</tr>
<tr>
<td>Minor, self-limited</td>
<td>12 (2.3%)</td>
</tr>
<tr>
<td>Major(^b)</td>
<td>5 (1.0%)</td>
</tr>
</tbody>
</table>

\(^b\) indicates complications that required medical attention or intervention.

De Gottardi, et al., Clinical Gastro Hepatology, 2009 (7), 906-909
Post Procedure Leakage

- Ostomy bag - can lead to secondary infection
- Lay patient on opposite flank
- Dry completely
- Use skin adhesive to bond site
- If refractory, consider figure of 8 stitch
Prospective Study on Complications

- Higher risk in those patients:
  - Undergoing therapeutic tap
  - Child-Pugh Class C
  - Platelet count < 50,000
  - Underlying alcoholic liver disease

- INR elevation did not increase risk
  - Pay attention to platelet ct and fibrinogen
    - Treat plts < 50K with platelet transfusion
    - Treat fibrinogen < 120 with cryoprecipitate
    - Avoid FFP as much as possible

De Gottardi, et al., Clinical Gastro Hepatology, 2009 (7), 906-909
Malnutrition in Cirrhosis

- 20% of compensated cirrhotic patients
- 60% of decompensated cirrhotic patients

- Affects short term mortality
- Affects clinical outcomes

Campillo, et al., Nutrition, 2003 (19), 515-521
Malnutrition in Cirrhosis

- Followed all cirrhosis admissions for 18 months
  - 396 patients
- Higher mortality in those patients:
  - Older age
  - More severe liver failure
  - Lower caloric intake
  - Lower protein intake
  - Higher Cr levels
  - Higher CRP levels

Campillo, et al., Nutrition, 2003 (19), 515-521
Malnutrition in Cirrhosis

- Highest nutritional deficits had tense ascites
  - Increased expenditure
  - Depleted body protein
  - Decreased dietary intake

- May have role for enteral tube feeding
- Often patient discomfort precludes nasal feeding tube

Campillo, et al., Nutrition, 2003 (19), 515-521
Case #2 – Appropriate Diet

- 45F with HCV cirrhosis with asterixis
- Admitted to the hospital for fever work up
- History of severe encephalopathy and SBP
- What diet is appropriate for this admission?

What diet is appropriate for this admission?

A. Low fat diet
B. Low sodium diet
C. Low protein diet
D. Low flavor diet
Table 2  Results of a questionnaire sent through the website of the Italian Society of Gastroenterology and Hepatology in 2005

<table>
<thead>
<tr>
<th>Proposed questions</th>
<th>Proposed answers</th>
<th>Percentages of physicians preferences</th>
</tr>
</thead>
<tbody>
<tr>
<td>“How many proteins do you prescribe in the hospital diet when a cirrhotic patient admitted for severe hepatic encephalopathy improves and is able of eating?”</td>
<td>&gt;50 g/protein/day</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td>30–50 g/protein/day</td>
<td>42%</td>
</tr>
<tr>
<td></td>
<td>&lt;30 g/protein/day</td>
<td>52%</td>
</tr>
<tr>
<td>“How many proteins do you prescribe in the hospital diet when a cirrhotic patient is admitted for mild hepatic encephalopathy?”</td>
<td>&gt;50 g/protein/day</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td>30–50 g/protein/day</td>
<td>72%</td>
</tr>
<tr>
<td></td>
<td>&lt;30 g/protein/day</td>
<td>3%</td>
</tr>
</tbody>
</table>
Nutritional Management

- Cirrhosis depletes body mass
- Liver unable to derive glucose
- Decreased ability for gluconeogenesis
- Glucose thus derived from muscle and adipose catabolism
- Increases protein requirements
PEG tubes in Cirrhosis

- Series of 26 patients, 17 with ascites (65%)
- 10 patients died within 30 days (38.5%)
- 9 of these patients had ascites

- High rate of complications in cirrhotic patients
- Those without ascites may be less risky
# PEG tubes in Cirrhosis

## Difficulties of PEG Placement with Ascites

<table>
<thead>
<tr>
<th>Difficulty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apposition of the stomach and abdominal wall more challenging</td>
</tr>
<tr>
<td>Impaired tract formation and healing</td>
</tr>
<tr>
<td>Reaccumulation and catheter dislodgement</td>
</tr>
<tr>
<td>Leakage of ascites</td>
</tr>
<tr>
<td>Increased risk of infection</td>
</tr>
<tr>
<td>Increased risk of bleeding</td>
</tr>
</tbody>
</table>
## PEG tubes in Cirrhosis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Type</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kynci et al</td>
<td>Case report</td>
<td>Albumin, mannitol and furosemide Topical nitropaste to decrease portal pressure Ultrasound guided paracentesis on the day of PEG placement</td>
</tr>
<tr>
<td>Höroldt et al</td>
<td>Case report</td>
<td>Abdominal ultrasound during PEG placement to identify an area without varices</td>
</tr>
<tr>
<td>Pothuri et al</td>
<td>Case series of 94, including 59 with ascites</td>
<td>Pre-PEG paracentesis</td>
</tr>
<tr>
<td>Wejda et al</td>
<td>Case series of 4</td>
<td>3 suture triangle gastropexy during PEG placement or several days after placement for new onset ascites</td>
</tr>
</tbody>
</table>

## Alternatives to PEGs in Cirrhosis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Type</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al</td>
<td>Case series of 9</td>
<td>Radiologic gastrostomy with pre-procedural paracentesis</td>
</tr>
<tr>
<td>Ryan et al</td>
<td>Case series of 45</td>
<td>Radiologic gastrostomy with gastropexy and ultrasound every 2-5 days for 4 weeks to monitor ascites reaccumulation</td>
</tr>
<tr>
<td>Ho et al</td>
<td>Case series of 400, unspecified number with ascites</td>
<td>Radiologic gastrostomy with pre-procedural paracentesis, stomach insufflation and gastropexy</td>
</tr>
<tr>
<td>Oishi et al</td>
<td>Case series of 13</td>
<td>PTEG (percutaneous transesophageal gastrostomy) using external ultrasound of the neck and fluoroscopy to verify placement</td>
</tr>
<tr>
<td>Udomsawae ngsup et al</td>
<td>Case series of 17</td>
<td>PTEG as Oishi et al describe</td>
</tr>
</tbody>
</table>
Case #3: Hepatic Encephalopathy

- A 52 year old woman with known HCV related cirrhosis presents to your office with new-onset confusion reported by her daughter. She reports having difficulty with getting lost while driving twice in the last week and forgetting to pick up her grandchild two days ago. She was recently initiated on temazepam for insomnia; now she sleeps for several hours during the day. She was also started on oxycodone for back pain related to a muscle strain, and has been constipated. Her daughter reports that her handwriting has noticeably worsened over this same period and she has been dropping items. The patient is alert but disoriented to time and latent in responding to questions. She has asterixis on examination.
Hepatic Encephalopathy - Stages

- **Stage I**
  - Mild confusion, day/night reversal, altered mood, no asterixis

- **Stage II**
  - Drowsy, inappropriate behavior, + asterixis

- **Stage III**
  - Extremely drowsy, barely able to speak and obey simple commands

- **Stage IV**
  - Coma, sometimes able to respond to painful stimuli
Hepatic Encephalopathy - Physiology

Hepatic Encephalopathy - Causes

HE: precipitating factors

- Protein excess
- Trauma
- Infections
- GI bleeding
- Acidosis
- Hyponatraemia
- Sedatives
- Diuretics

HE-relevant components:
- ammonia
- benzodiazepines
- hyponatraemia
- inflammatory cytokines

Astrocyte swelling oxidative stress

True or False:

Serum ammonia levels are the most effective guide to adjusting therapy in HE?

A. True
B. False
Ammonia Level in HE

- Nicolao et al., 2003
  - 17 patients followed with HE resolved
  - Serum ammonia levels did NOT decrease
  - Sometimes levels increased with HE resolution

- Conclusion
  - Serum ammonia levels limited use for diagnosis or clinical management

Nicolao et al., Journal of Hepatology, 2003, 38, 441-446.
Ammonia Level in HE

Kundra et al., 2005

- Evaluated 20 patients with CLD
- Stage II mean ammonia level - 72.3
- Stage III mean ammonia level - 58.7
- Stage IV mean ammonia level - 42.0

Conclusion

- Ammonia levels of no utility in diagnosis or management of HE

Kundra et al., Clinical Biochemistry, 2005, 38, 696-699.
Ammonia Level - Utility?

- Carl Berg: “The only confusion an ammonia level measures is the confusion of the provider ordering that test for encephalopathy.”

- UVA Hepatic Encephalopathy Protocol
- Lactulose enemas in Stage III-IV
What is the best initial choice for treatment of intermittent musculoskeletal or abdominal pain in a cirrhosis patient with portal HTN?

A. Ibuprofen
B. Hydrocodone
C. Fentanyl
D. Tramadol
E. Acetaminophen
Pain Medication in Cirrhosis

- Issues with clearance
- Altered metabolism
- 3 modes of metabolism, often hindered:
  - P450 Pathway
  - Conjugation
  - Biliary Excretion

- Tylenol - up to 2g per day?
  - Increased risk of hepatotoxicity in chronic alcohol users/abusers
NSAIDs in Cirrhosis

- NSAIDs heavily protein bound
- Elevated free levels in cirrhosis
- Renal Impairment - decreased renal artery perfusion due to effects on prostaglandins, may increase fluid retention (ascites, edema) as well
- Increased bleeding risk with thrombocytopenia due to platelet effects
## Opioids in Cirrhosis

### TABLE 2. Opioid Analgesic Metabolism

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half-life (h)</th>
<th>Protein binding (%)</th>
<th>Hepatic metabolism</th>
<th>Special note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>4-6</td>
<td>7</td>
<td>CYP2D6</td>
<td>Metabolized to morphine in liver; ceiling effect; serum levels unpredictable</td>
</tr>
<tr>
<td>Morphine</td>
<td>3-12</td>
<td>35</td>
<td>Glucuronidation</td>
<td>Metabolite increases toxicity in patients with renal failure; adjust dose in these patients</td>
</tr>
<tr>
<td>Meperidine</td>
<td>2-4</td>
<td>70</td>
<td>CYP2B6, 3A4</td>
<td>Avoid in patients with renal failure; increased bioavailability of CNS active metabolite ($t_1/2 = 15-30$ h) in patients with renal/liver disease; avoid in patients with liver impairment</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1-3</td>
<td>15</td>
<td>Glucuronidation</td>
<td>Consider dose reduction in patients with liver impairment; safe to use in those with renal failure</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>3-4</td>
<td>7</td>
<td>CYP2D6</td>
<td>Active metabolite is hydromorphone</td>
</tr>
<tr>
<td>Fentanyl IV, patch</td>
<td>1-3</td>
<td>80</td>
<td>CYP3A4</td>
<td>Lipid soluble: stores in fat and muscle; continuous infusion = prolonged sedation; less histamine release, less hemodynamic disturbance</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>2-12</td>
<td>45</td>
<td>CYP3A4, 2D6</td>
<td>Multiple metabolite levels unpredictable; reduce dose and frequency in patients with liver impairment</td>
</tr>
<tr>
<td>Tramadol</td>
<td>7</td>
<td>20</td>
<td>CYP3A4, 2D6, and glucuronidation</td>
<td>Reduce dose and frequency in patients with renal and liver impairment</td>
</tr>
<tr>
<td>Methadone</td>
<td>8-24</td>
<td>80</td>
<td>CYP3A4, 2D6, several others</td>
<td>Consider dose reduction; equivalence ratios to methadone are dose-dependent (may range from 1:1 to 20:1)—cautious dose titration</td>
</tr>
</tbody>
</table>

CNS = central nervous system; CYP = cytochrome P450; IV = intravenous.
Preferred Opioids in Cirrhosis?

- **Tramadol**
  - Works on peripheral pain
  - Low affinity for opioid receptors
  - Less sedation effect
  - Lower potential for tolerance

- **Fentanyl or Hydromorphone**
  - Least affected by renal function
  - Order in lower doses and longer intervals
Pain Medication Algorithm

Start with Acetaminophen

Try Tramadol

Use opiates only for intractable pain and minimize

For intractable pain, consider:
Hydromorphone, 1 mg orally every 4 h
or
Fentanyl, 12.5 μg topically every 72 h

Do not combine these agents with tramadol

Clinical Pearls

- **Paracentesis**
  - Remember albumin replacement in LVP or SBP
  - Most complications self-limiting
  - Avoid ostomy bag if leaking and use skin adhesive and lay on opposite flank

- **Malnutrition**
  - Avoid PEG tubes in cirrhosis, especially in presence of ascites
  - Avoid low protein diets – maintain normal protein intake to circumvent muscle mass loss
  - Consider NG tube feeds early
Clinical Pearls

- Hepatic Encephalopathy
  - Diagnosis of underlying cause imperative
  - Ammonia level of limited to no use – asterixis and longitudinal care is best guide

- Pain Medication
  - Acetaminophen in limited doses as initial agent
  - Tramadol as 2nd-line in those with contraindications
  - Consider fentanyl or hydromorphone if opioid needed in lower doses, less frequency -- minimize
  - Non-opioid alternatives if neuropathic
The management of hospitalized patients with cirrhosis: the Mount Sinai experience and a guide for hospitalists.

Coagulation in liver disease: a guide for the clinician.
Questions?