ASCITES AND HYPONATREMIA IN LIVER CIRRHOSIS: HOW AND WHEN TO INTERVENE

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Liver Cirrhosis: leading cause of death in general population worldwide (e.g. 12th leading cause of mortality in USA)

Liver Transplantation: the only approach that reliably improves duration and quality of life

End-stage Liver Disease: primary focus is to keep patients alive and in the most stable condition (very challenging!)
Natural History of Liver Cirrhosis

Chronic Liver Disease
(Viral, ETOH, Fatty liver)

Compensated Liver Cirrhosis (median survival 12 years)

5-7 %/ year

 Decompensated Liver Cirrhosis (median survival 2 years)
Jaundice, Variceal bleeding, Ascites, Hepatic encephalopathy, HRS or HCC

Death
Ascites is one of the complications that mark the transition from a compensated to a decompensated stage of liver cirrhosis.
### Liver Cirrhosis

**D’ Amico’s Clinical Staging & Prognostication**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Condition</th>
<th>1 year mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>No varices, No ascites</td>
<td>1%</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Varices (non-bleeding), No ascites</td>
<td>3-4%</td>
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<tr>
<td>Stage 3</td>
<td>Varices, Ascites</td>
<td>20%</td>
</tr>
<tr>
<td>Stage 4</td>
<td>Bleeding varices, Ascites</td>
<td>50%</td>
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</tbody>
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J Hepatology 2006
44: 217-231
Clinical Symptoms of Liver-Related Ascites

1. Increase in abdominal girth
2. Abdominal fullness, discomfort or ache
3. Shortness of breath
4. Early satiation
5. Sense of reduced mobility
Severity of Ascites

Grade I: 100mL (normal 25-50mL) by US studies

Grade II: 1000mL detected by P.E.
- sagging flanks
- shifting dullness
- fluid wave
- Puddle sign

Grade III: liters of ascitic fluid
- “Tense” ascites, grossly distended abdomen
Patients with New Onset Ascites

1. History
2. Physical examination *
   - spider angiomas
   - palmar erythema
   - muscle wasting
   - jaundice
   - signs of portal hypertension (e.g. splenomegaly, abdominal wall collaterals)
   - palpable left lobe of liver

* Pathognomonic of liver cirrhosis
New-Onset Ascites

Diagnostic Paracentesis
Tests Performed in Diagnostic Paracentesis

Gross appearance
Total protein
Albumin (with simultaneous serum albumin)
WBC & differential count
Bacteriological cultures
Cytology

* Amylase (if pancreatic ascites is suspected)
* AFB staining & culture (if peritoneal TB is suspected)
* Glucose & LDH (if secondary peritonitis is suspected)
* Triglycerides (milky appearance e.g. chylous)
* RBC (bloody)

* Special tests
Pathogenesis of Cirrhosis

1. Cirrhosis
   - ↑ intrahepatic resistance
   - Portal hypertension
     - Splanchnic/Systemic Vasodilatation
       - ↓ Effective arterial blood volume
         - Activation of neurohormonal systems
           - 2. Na retention
           - 3. Water retention
           - 4. Renal vasoconstriction
             - Refractory ascites
             - Hyponatremia
             - Hepatorenal syndrome

Ascites

Na retention
Water retention
Renal vasoconstriction
Refractory ascites
Hyponatremia
Hepatorenal syndrome
Serum-Ascites Albumin Gradient

SAAG >1.1g/L
- CHON <2.5g/L
  - Cirrhosis
  - CTscan
  - EGD (varices)

- CHON ≥ 2.5g/L
  - Post-hepatic process
  - Cardiac Echo
  - Hepatic V Doppler

SAAG <1.1g/L
- Peritoneal Process
- Cytology
- AFB
- Adenosine deaminase
  - CTscan

Diagnosis still uncertain, values contradictory or borderline

- HVPG± TJLI (transjugular liver biopsy)
- Laparoscopy ± Peritoneal biopsy
Hyperammonemia

- Increased glutamine synthesis
- ↑ intracellular osmolality
- Water shift from extracellular space
- Reduction of intracellular osmolytes
- Astrocyte swelling
- Astrocyte dysfunction
- Factors increasing ammonic synthesis; progressive hyponatremia

Hypogonadism

- ↓ extracellular osmolality
- Water shift from extracellular space
- Astrocyte dysfunction

Hepatic encephalopathy

Presence of Hyponatremia is associated with increased morbidity

Site of Action of Different Therapies for Ascites

- **CIRRHOSIS**
  - ↑ Intrahepatic resistance
  - Portal hypertension
  - Splanchnic/systemic vasodilatation
  - ↓ effective arterial blood volume
  - Activation of Neurohormonal systems
  - Sodium retention
  - Ascites

- **Liver Transplant**
  - TIPS
  - Vasoconstrictors?
  - Albumin
  - Spironolactone
  - Furosemide, V2 antagonists
  - LVP, PVS
Patients with Cirrhosis and New Ascites

- Sodium restriction (2gm Na/day = 5.2gm dietary salt)

Concomitant:
- GI hemorrhage
- HE
- Renal deficiency
- SBP/Infection

Yes → Tense ascites

Yes → Single LVP * : albumin

No → Spironolactone 100mg ± Furosemide 40mg

Weight loss 1-1.5kg/week → Continue same dose

Weight loss < 1kg/wk → Increase dose (x2) every 1-2 wks

Weight loss > 0.5kg/day ± complication → Decrease dose or discontinue

Ascites eliminated → Titrate down diuretics

Assess Transplant Candidacy

Resolve complication before specific treatment

- Weight loss < 1kg/wk
- Weight loss > 0.5kg/day ± complication

* large volume paracentesis
Refractory Ascites

LVP + I.V. albumin (6-8g/L)

Requires > 2-3x/month

TB >3mg/L or CTP >11

Yes

Transplant candidate

No

uNa >20mg/L

Yes

Continue diuretics

No

No diuretics

TIPS

? PVS

Continue LVP until transplant
1. Fluid restriction
2. Aldosterone antagonists
3. Loop diuretics
4. Vasopressin receptor antagonist antagonists

Treatment of Hypervolemic Hyponatremia in Cirrhosis
Collecting Principal Duct Cell

Urinary Space

- H2O
- AP2
- PKA
- cAMP
- ATP
- V2 receptor
- V2 receptor antagonist (S)

Basolateral space

- AVP
- G protein
- Adenyl cyclase
- S

Wong, F. Hyponatremia in Cirrhosis. Hepatology 2006; 44: 1535-42
Six Vaptans

1. Mozavaptan (OPC-31260)
2. Lixivaptan (VPA-985)
3. Tolvaptan (OPC-40161)
4. SPD556 (M0002/RWJ 351647)
5. Satavaptan (No longer being developed)
6. Conivapatan (V1 & V2 receptor antagonist)

Very effective in normalization of Na concentration
*** Recurrence of hyponatremia when stopped
No long term data on safety & efficacy
High cost
Can not be recommended for general use
1. Ascites and dilutional hyponatremia are frequent complications in cirrhotic patients and are associated with poor renal function and poor quality of life.

2. Aldosterone antagonists (spironolactone) and loop diuretics (furosemide) are the treatment of choice.

3. Some non-responders to conventional treatment, new therapeutic options are necessary e.g. Vaptans.

Thank you
Pathogenesis of Hyponatremia in Cirrhosis

- Decompensated Liver Disease & PHTN
- Release of Vasodilators e.g. NO
- Decreased SVR especially splanchnic & renal circulation
- Imbalance between vascular capacity & plasma volume
- Decrease renal perfusion
- Increased RAS
- Salt & Fluid Retention
- Ascites formation & Fluid retention
- Increased aquaporin 2 activity independent of AVP activity in collecting ducts of kidneys
- Impaired free water excretion and fluid retention