Cirrhosis: Ascites, Encephalopathy and Pulmonary Features

W.D. Carey, M.D
Professor of Medicine
Cleveland Clinic Lerner College of Medicine
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Consequences of Portal Hypertension and Cirrhosis
Case # 1

A previously stable outpatient continues to feel well except for increased abdominal girth and an unexplained 25 lb weight gain. You determine she has ascites. Which is the best description of her hemodynamic state

1. Low-normal cardiac output
2. Hyperdynamic circulation
3. Decreased intravascular volume
4. None of the above

Best answer: 2

Cirrhotics have a hyperdynamic circulation. Ascites forms despite normal or increased intravascular volume. Cardiac output is normal or high.
Causes of Ascites

- Cirrhosis
- Non-Cirrhotic liver disease
  - Alcoholic hepatitis
  - Fulminant liver failure
- Hepatic Vein Outflow
  - Budd Chiari
  - Right heart failure
  - Constrictive pericarditis
- Peritoneal Disease
  - Neoplasm
  - TBC
- Nephrotic syndrome/ Renal failure
- Lymphatic obstruction
- Sinusoidal obstruction
- Myxedema
- Pancreatitis

Pathophysiology of ascites
Starling’s Forces
A balance between intravascular and interstitial oncotic and hydrostatic pressures

\[ J_v = k_f \left[ (P_C - P_I) - \sigma (\Pi_I - \Pi_P) \right] \]

where:
- \( J_v \): Net fluid flux
- \( P_f \): Fibrinogen concentration
- \( P_C \): Capillary oncotic pressure
- \( P_I \): Interstitial hydrostatic pressure
- \( \sigma \): Reflection coefficient
- \( \Pi_I \): Interstitial oncotic pressure
- \( \Pi_P \): Plasma oncotic pressure

\[ \Pi_I - \Pi_P \] is the net driving pressure

Sodium Retention and ascites formation in dogs with experimental portal cirrhosis

Stages of Ascites in Cirrhosis

Subtle sodium retention
Obvious sodium retention
Avid Sodium retention
Functional Renal failure

Pre-Ascites
Responsive Ascites
Refractory Ascites
Hepatorenal Syndrome

Decompensation
Systemic arterial vasodilation
Renal vasoconstriction
RAS activation

= Risk for SBP

Adapted from Wong J Gastro & hepatology "accepted article"

Evaluation of Ascites

- Take a history
- Do an exam
  - Heart, neck
  - Stigmata of liver disease
  - Be sure it is ascites (obesity, distended bladder, pregnancy, polycystic disease)
  - Plan a paracentesis site
- Basic labs
**Ascitic Fluid Studies**

**Initial or Changed Clinical State**

- Always
  - Cell count and differential
  - Albumin
  - Total protein
  - Gram stain
  - Culture (blood culture bottles at bedside)
- As indicated
  - Amylase/lipase
  - Cytology
  - Triglycerides (if milky)
  - AFB smear and culture

**Routine subsequent LVP**

- Always
  - Cell count and differential

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**SAAG**

Serum-ascites albumin gradient

- **High Gradient**
  > 1.1
  - Portal hypertension
    - Cirrhosis* (including SBP)
    - Budd Chiari
    - Right heart failure

- **Low Gradient**
  < 1.1
  - Infection (not SBP)
  - Nephrosis
  - Malignancy

* Total protein usually < 1 gm/dl in cirrhosis and > 2.5 gm/dl in all others
Treatment of Cirrhotic Ascites

• Salt restriction
  – 2 gm sodium
• Treat underlying disease
  – Alcoholic liver disease
  – Hepatitis B
• Diuretics
  – Distal tubular agent (e.g., spironolactone)
  – Loop agent (e.g. furosemide)
• TIPS

Refractory Ascites

• Diuretic resistant
  – Poor control despite demonstrated dietary sodium restriction and maximum doses of diuretic
• Diuretic intolerant
  – Renal dysfunction or severe electrolyte disturbance
Refractory Ascites

- **Diuretic resistant**
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- **Diuretic intolerant**
  - Renal dysfunction or severe electrolyte disturbance

Tests to consider

- **Urine sodium excretion ON diuretic**
  - 24 hour urine
    - Cumbersome
    - Track complete collection with urine creatinine (men > 15 and women > 10 mg/kg/day)
  - Random urine Na
    - Very low or very high helpful
    - Urine [Na]/[K] if > 1 suggests adequate urine Na excretion. If < 1 suggest RA

Paracentesis
Sodium Retention and ascites formation in dogs with experimental portal cirrhosis

Effect of Large volume paracentesis on plasma volume

When no sodium in diet

Weight decreases

No change in ascitic volume

When 150mEq sodium in diet

Weight increases

ascitic volume restored

Paracentesis-Induced Circulatory Dysfunction (PICD)

Increase in plasma renin lasting several days after paracentesis

- Those who develop it after total paracentesis have a shorter time to readmission (1.3 vs 3.5 months) and shorter survival (9.3 vs 16.9 months)
- Serum creatinine, sodium, and Child-Pugh score at inclusion, and postparacentesis circulatory dysfunction were independent predictors of survival.
  - PPCD after dextran 24%
  - Polygeline 38%
  - Albumin 19%

Ginès A
Gastro1996;111:1002-10
Randomized comparative study of therapeutic paracentesis with and without intravenous albumin in cirrhosis

105 with tense ascites
• Group 1: LVP 4-6 L/day until gone
Or
• Group 2. Same plus 40 gm albumin
• Discharge on diuretics
• Followed for. Repeat Rx for recurrences

• Survival similar
• Group 1 more likely to develop
  – Clinically silent renal impairment or severe hyponatremia
  – Such development was an independent predictor of mortality

Gines et al
Gastro:1493-502

Paracentesis-Induced Circulatory Dysfunction (PICD)

• Occurs in
  – 7% when LVP < 6 liters
  – 37% with total paracentesis
• Does not occur after every LVP
• Not every case of PICD produces renal effects (~40%)
• Renal impairment may occur after LVP without PICD (~11%)
Post Paracentesis Syndrome

“No study [demonstrates] decreased life expectancy in patients who are given no plasma expander…While more studies are awaited, it is reasonable although not mandatory to give it for paracentesis greater than 5 liters”

Recommendation 15: For LVP, an albumin infusion of 6-8g/L can be considered.

Runyon
AASLD Practice Guideline
Hepatology 2009: 2087

Transjugular intrahepatic portosystemic shunt - TIPS
TIPS

- Functions like a portocaval shunt
- Reduces portal pressure, the central factor in ascites formation
- Enhanced urine [Na] excretion often delayed for weeks
- Ascites resolution in 2/3
  - Often improved renal function, nutritional status, and QOL

TIPS vs LVP

- Five RCT show TIPS superiority in ascites control at expense of more HE
- High maintenance – stenosis
- Polytetrafluoroethylene coated stents are superior to bare metal stents
TIPS vs. LVP

Meta-analysis of Individual Patient Data
– 4 studies total 305 patients (149 TIPS)
– Outcomes favoring TIPS:
  • Need for paracentesis, recurrence of tense ascites, survival
– Outcomes favoring LVP
  • Average # episodes of HE
    – Older age, low mean arterial pressure slightly predictive in TIPS subgroup

Salerno et al
Gastro 2007: 133: 825

TIPS for Ascites

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>PSE</th>
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<tbody>
<tr>
<td></td>
<td>TIPS</td>
<td>LVP</td>
</tr>
<tr>
<td>N=60</td>
<td>61%</td>
<td>18%</td>
</tr>
<tr>
<td>N=70</td>
<td>51%</td>
<td>17%</td>
</tr>
<tr>
<td>N=109</td>
<td>58%</td>
<td>16%</td>
</tr>
<tr>
<td>N=66*</td>
<td>79%</td>
<td>42%</td>
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</tbody>
</table>

* Study showed survival advantage of TIPS
TIPS vs. LVP

Meta-analysis of Individual Patient Data
Survival Analysis
Factors predicting increased mortality
1. Allocation to LVP
2. Older age
3. Higher bilirubin
4. Lower [Na]

Salerno et al
Gastro 2007: 133: 825

TIPS vs. LVP

Meta-analysis of Individual Patient Data
Survival Analysis – Effect of MELD
Mortality for both LVP and TIPS increased with higher MELD

Estimated survival by MELD
• < 11
• 11-18
• >18
ALL FAVORED TIPS

Salerno et al
Gastro 2007: 133: 825
**Spontaneous Bacterial Peritonitis**

**SBP Pearls**

- Most common clinical sign:
  - Any change in clinical status
  - Up to 30% have no symptoms or signs

- Most common organisms
  - Negative culture: 50%
  - Gram negative:
    - E coli: 45%
    - K. pneumoniae: 15%
    - Enterobacter: 5%
  - Gram positive:
    - Pneumococcus: 15%
    - Strep viridans: 10%
    - Enterococcus: 5%

- If anaerobes, polymicrobial, or fungal think secondary peritonitis
Spontaneous Bacterial Peritonitis

Neutrocytic
> 250 PMNs with or without positive gram stain/culture

Non-neutrocytic Bacterascites
< 250PMNs but positive culture
Treat even though colonization may clear spontaneously

Case # 2

According to evidence-based medicine, which of the following is true regarding treatment of SBP in a cirrhotic:

1. Treatment duration is not influenced by initial bacteremia
2. IV antibiotics are required
3. 14 days of treatment is recommended
4. IV albumin should always be given
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Best answer: 1

In the landmark study demonstrating five days of antibiotics are as good as 10 the presence of bacteremia did not influence the success of five day treatment. IV albumin is recommended for those with renal impairment and those with a bilirubin > 4 mg/dl. Oral quinolones seem to be as effective as IV antibiotics. All should be treated in hospital.

SBP Treatment

• Cefotaxime or similar 3rd generation cephalosporin covers 95% of flora including the top 3
  – E. coli
  – Klebsiella p.
  – Pneumococcus
• Five days is as good as 10
SBP Treatment

Re tap during RX?

- 16 patients with SBP: Recurrence occurred in only 1/11 patient when 48 hour ascitic fluid PMN cell count < 250/mm3.

- Recurrence in all (5) who had 48 hour ascitic fluid PMN cell count ≥ 250/mm3, 48 hours after the therapy was started.

- CONCLUSIONS: By monitoring ascitic fluid PMN cell count it seems to be possible to determine the efficacy and optimal duration of cefotaxime therapy in patients.

(Hepatogastroenterology 2000;47:1360-3 )

AASLD Guideline is mute in recommendation but text states it need not be done unless atypical features or response

SBP Treatment

Oral Therapy?

- Ofloxacin 400mg BID for average of 8 days as effective as cefotaxime
  - Exclusion: shock, vomiting, or advanced PSE, or creatinine > 3mg/dl

- All treated in hospital

AASLD Guideline: This treatment OK if no exclusion criteria, no prior exposure To quinolones.
SBP Treatment

IV Albumin for all SBP?
– RCT: cefotaxime with or without albumin (Sort NEJM 1999; 341: 403)
  • 1.5 g/Kg body weight day 1 and 1.0 g/kg on day 3
– Albumin group mortality 10% (vs 29%)
– Post hoc analysis - benefit seen in those with renal insufficiency

AASLD Guideline: Use albumin if creatinine > 1, BUN > 30, or bilirubin > 4.

SBP Treatment

Should those with positive blood cultures receive more than 5 days?
– No evidence those with bacteremia need longer Rx (Runyon et al Gastroenterology 1991; 100:1737)

AASLD Guideline is mute
Hepatorenal Syndrome

- HRS type I – rapidly progressive
- HRS type 2 - chronic, more slowly progressive
Hepatorenal Syndrome

1. Cirrhosis and ascites
2. Creatinine > 1.5mg/dl
3. No shock
4. No decrease to < 1.5mg/dl after 2 days of withdrawal of diuretics and volume expansion with D5NS or albumin*
5. No current or recent Rx with nephrotoxic drugs
6. Urine protein < 500mg/day, and RBC < 50 hpf
7. Normal renal us

* Suggested 1g/kg bw up to 100 gm per day

HRS Treatment Options

- Dialysis
- Pharmacological
  - Albumin
  - Midodrine
  - Octreotide
  - Terlipressin
HRS Treatment (US)

Midodrine plus octreotide plus albumin
midodrine up to 12.5mg po TID
octreotide 200ug sc TID
albumin 10-20g IV per day for 20 days

Practice Guideline: Albumin infusions plus vasoactive drugs such as octreotide and midodrine should be considered in the treatment of type I HRS

HRS Treatment (elsewhere)

Consider terlipressin with albumin
10 adequate RCT considered in meta-analysis
Primary end point – improved renal function
Meta-analysis shows benefit of terlipressin compared regimens without
Survival benefit not apparent

Glud et al.
Hepatology 2010; 51:576-584
Treatment of Hyponatremia in Cirrhosis

Vasopressin Actions
FDA Approved V2 Vasopressin Antagonists - Vaptans

Conivaptan (Vaprisol®) IV only
Tolvaptan (Samsca®) Oral only

A brief History of Vaptans in Cirrhosis

- 1998 Inoue et al: 8 cirrhotics with Na =138; 24 hours; aquareisis. OPC-31260 (precursor to tolvaptan)
- 2002: Guyader et al: oral V produces aquareisis –short term (hours)
- 2003 Wong et al VPA 985 33 cirrhotics
  - 125 > 132 over 7 days
- 2009 O’Leary et al: retrospective 24 cirrhotics low [Na] max 4 day study; increase of ≥5 mEq/L in 60% by day 4
Utility of Satavaptan in the Management of Cirrhotic Ascites

Satavapatan versus placebo
1. In combination with diuretics in management of ascites NOT requiring large volume paracentesis (LVP)
2. In combination with diuretics in prevention of recurrent ascites
3. As monotherapy (no diuretics) in prevention of recurrent ascites after LVP

Wong et al
Gut 2011

Vaptan Conclusions

• Improves hyponatremia
• ~ $300 per pill
• Has little positive effect on important outcome measures
• May be dangerous in some circumstances
• Alone or in combination with diuretics is not clinically beneficial in the long term management of ascites in cirrhosis.
Case # 3

What pathophysiologic process sets the stage for hepatic encephalopathy in the cirrhotic:

1. Hepatic venous outflow obstruction
2. Poor hepatic function
3. Shunting of blood around the liver
4. Toxic effects of branched chain amino acids

Best answer: 3

Creation of a portacaval shunt (Eck fistula) in an animal with a normal liver will produce hepatic encephalopathy. A TIPS may have the same effect in humans even when liver synthetic function is well-maintained. Toxins present in the portal vein are rapidly taken up and detoxified. In portal hypertension some portal blood bypasses the liver. Branched chain amino acids are not neurotoxic (aromatic amino acids may be).
Pathogenesis of Hepatic Encephalopathy

- It all begins with shunting of portal blood around the liver
- Toxins (e.g., ammonia, mercaptans)
- Enhanced GABAergic neurotransmission
  - Gamma aminobutyric acid from glutamine acid, from upregulation of glutamine synthetase
  - Augmented by benzodiazepine receptor ligands
- False neurotransmitters (aromatic amino acids mimic adrenergic neurotransmitters)
Clinical Stages of Hepatic Encephalopathy

- **Stage 0** (aka – Subclinical, minimal encephalopathy
  - Normal exam; psychometric tests abnormal
  - Driving impaired
- **Stage 1**
  - Impaired attention, personality changes
- **Stage 2**
  - Drowsiness, asterixis
- **Stage 3**
  - Confusion, disorientation, somnolence, asterixis
- **Stage 4**
  - Stupor, coma

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Table 10–16. Common precipitants of hepatic encephalopathy.¹

<table>
<thead>
<tr>
<th>Increased nitrogen load</th>
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<tbody>
<tr>
<td>Gastrointestinal bleeding</td>
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<tr>
<td>Excess dietary protein</td>
</tr>
<tr>
<td>Azotemia</td>
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<tr>
<td>Constipation</td>
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<tr>
<td>Electrolyte imbalance</td>
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<tr>
<td>Hypokalemia</td>
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<tr>
<td>Alkalosis</td>
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<tr>
<td>Hypoxia</td>
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<tr>
<td>Hypovolemia</td>
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<tr>
<td>Drugs</td>
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<tr>
<td>Opioids, tranquilizers, sedatives</td>
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<tr>
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<tr>
<td>Infection</td>
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<tr>
<td>Surgery</td>
</tr>
<tr>
<td>Superimposed acute liver disease</td>
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<tr>
<td>Progressive liver disease</td>
</tr>
</tbody>
</table>

Treatment of Hepatic Encephalopathy

- Find and treat the cause (50%)
- Lactulose
- Non absorbable antibiotics
  - Rifaximin
  - neomycin
- Short term protein restriction
- Long term: ingest the right protein
  - Avoid red meat

Pulmonary Manifestations of Cirrhosis

- Pleural Effusion (Hepatic hydrothorax): right sided 75%)
  - Defects in diaphragm
  - Key feature: abnormal CXR
  - Rx: as per ascites plus: thoracentesis, pleurodesis, TIPS (best)
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• Portopulmonary hypertension
  – Obliteration of pulmonary arterioles
  – Key feature: ECHO elevated RV pressures
  – Rx: prostacyclin analogues, phosphodiesterase inhibitors, OLT if mild-moderate [mean RVP <35 mild; RVSP >50 severe – no OLT option]

• Hepatopulmonary Syndrome
  – Pulmonary pre-capillary dilation > AV shunting
  – Key feature: deoxygenation; abnormal agitated bubble study after 3 beats (< 3 beats = intracardiac shunt, e.g., PFO)
  – Rx: oxygen, OLT
Thank You