Management of Ascites and Fluid Overload

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Case presentation

• A 40-year-old male with h/o HCV and cirrhosis presents with increasing abdominal distension. On examination, he has flank fullness and moderately tense ascites. Laboratory studies show:
  • Hgb: 11 gm/dl
  • WBC: 8000/mm3
  • Platelets: 70000/mm3
  • Bilirubin: 1.5 gm/dl
  • Albumin: 2.8 gm/dl
  • Creatinine: 1.4 mg/dl
  • Na: 133 meq/l
  • INR: 1.5
Question

• What is the best initial approach:
  – Na restriction and bed rest
  – Diuretics
  – Large volume paracentesis
  – Early TIPS

A rational basis for treating ascites

- Cirrhosis
- Sinusoidal portal hypertension
- Splanchnic arterial vasodilation
- Decreased effective circulating volume
- Activation of Na/H2O retention
- Renal vasoconstriction
- Renal adaptation

*Yes* compensated
*No* Refractory ascites
### Initial approach to ascites

<table>
<thead>
<tr>
<th>Approach</th>
<th>Details</th>
</tr>
</thead>
</table>
| **Na restriction + diuretics:** | - Na (88 meq/day)  
- use combination of loop-acting and distal acting diuretics when feasible |
| **Slow** | Does not affect survival |
| **Large volume paracentesis (LVP):** | - > 5 liters |
| **Fast** |  
- High rate of recurrence  
- Does not affect survival  
- Requires albumin infusion to prevent post paracentesis circulatory dysfunction |

### Question

- What is the most optimal approach for diuretic use:
  - furosemide alone
  - spironolactone alone
  - spironolactone and furosemide
  - amiloride
Renal physiology: back to basics

**Step 1:** Glomerular filtration

**Step 2:**
1. Isotonic Na reabsorption

**Step 3:**
\[ \text{Step 3: } \text{Cl} - \rightarrow + \text{Na} + \]

**Step 4:**
1. Na/K/H exchange
2. Aldosterone-regulated

**Step 5:**
\[ \text{H}^+ \text{Cl}^- \rightarrow \text{HCO}_3^- \]

Loop of Henle

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**Case continued**

- Patient started on Na restriction and spironolactone (100 mg/day) and a LVP is performed. Patient is discharged but returns after 5 days with tense ascites.
  - Bilirubin: 6 mg/dl
  - Albumin: 2.2 gm/dl
  - INR: 1.6
  - Creatinine: 2.4 mg/dl
Next best steps

• Increase spironolactone (200 mg/day)
• Add furosemide (40 mg/day)
• Place another TIPS
• LVP + i.v. albumin

Traditional coagulation parameters do not predict bleeding risk in cirrhotics

• INR, platelets, TEG do not predict ulcer or procedure related bleeding after EVL. (*Da Rocha et al, CGH, 2009*)

• INR, platelets do not predict peri- or post-paracentesis hemorrhage (*Grabau et al, Hepatology, 2004, Lin et al, Dig Liv Dis 2005*)
INR has no correlation with bleeding risk after procedures

<table>
<thead>
<tr>
<th>Reference/Procedure</th>
<th>Abnormal tests n/N</th>
<th>Normal tests n/N</th>
<th>Risk difference</th>
<th>95% CIs</th>
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</thead>
<tbody>
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<td>1/65</td>
<td>15/915</td>
<td>0.00 [-0.03, 0.02]</td>
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<tr>
<td>12 angiography</td>
<td>0/9</td>
<td>0/200</td>
<td>0.00 [-0.14, 0.14]</td>
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<td>3/28</td>
<td>28/219</td>
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<tr>
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<td>43/412</td>
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<tr>
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<td>0/27</td>
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<td>0.00 [-0.14, 0.14]</td>
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<tr>
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<td>4/100</td>
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<td>4/85</td>
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<tr>
<td>13 liver laparoscopy</td>
<td>0/29</td>
<td>1/50</td>
<td>-0.02 [-0.08, 0.05]</td>
<td></td>
</tr>
<tr>
<td>29 transjugular liver</td>
<td>0/112</td>
<td>0/45</td>
<td>0.00 [-0.03, 0.03]</td>
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<tr>
<td>14 transjugular liver</td>
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<td>0/19</td>
<td>0.00 [-0.06, 0.08]</td>
<td></td>
</tr>
<tr>
<td>31 transjugular liver</td>
<td>3/203</td>
<td>0/168</td>
<td>0.01 [-0.05, 0.03]</td>
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</tr>
<tr>
<td>23 pancreas/duodenum</td>
<td>1/9</td>
<td>1/9</td>
<td>-0.01 [-0.46, 0.44]</td>
<td></td>
</tr>
<tr>
<td>15 transjugular kidney</td>
<td>2/10</td>
<td>0/15</td>
<td>0.20 [-0.06, 0.46]</td>
<td></td>
</tr>
<tr>
<td>33 kidney biopsy</td>
<td>1/9</td>
<td>33/189</td>
<td>-0.19 [-0.41, 0.02]</td>
<td></td>
</tr>
</tbody>
</table>

Segal and Dzik, Transfusion, 2005, 45:1413-1425

How high can you go with diuretics?

- **Spironolactone:**
  - 100 mg
  - 200 mg
  - 300 mg
  - 400 mg
  - 500 mg

- **Furosemide:**
  - 40 mg
  - 80 mg
  - 120 mg
  - 160 mg
  - 200 mg
**Refractory Ascites**

**International Ascites Club Criteria**

- **Diuretic Resistant:** failure to lose at least 1.5 Kg/wk on:
  - 400 mg Spironolactone
  - 160 mg furosemide

- **Diuretic intractable:** failure to lose weight due to inability to use effective doses because of diuretic side effects.

**TIPS vs Taps**

*(impact on recurrence of ascites)*

- TIPS is better than taps
- TIPS used in addition to taps
- Standardized Na restriction not uniformly provided in all studies

*Albillos et al, J Hepatol 2005*
TIPS vs TAPS
(impact on rates of complications related to cirrhosis)

- No significant differences in the 2 largest studies
- Specifically, infection and sepsis rates were similar

Sanyal et al, Gastroenterology, 2003
Gines et al, Gastroenterology, 2002

Implantable Pump System

- ipump
- Peritoneal cavity
- Ascites
- Peritoneal catheter
- Bladder catheter
Case continued

- Patient returns after 4 weeks. The family reports that the patient is more forgetful and complains of increasing headaches. On examination he has asterixis.
- Labs show:
  - Bilirubin: 4 mg/dl
  - INR: 1.6
  - Creatinine: 1.5 mg/dl
  - Na: 125 meq/l

Prevalence of hyponatremia in subjects with cirrhosis

Angeli et al, Hepatology, 2006
Hyponatremia (impact on survival)

- Serum sodium $<130$ mEq/L
- Serum sodium $131-135$ mEq/L
- Serum sodium $>135$ mEq/L

3-month survival

- Probability $p=0.001$

How to treat hyponatremia

- Correct hypovolemia
- Decrease VP secretion
- Excrete more water-vaptans
- Restrict water

- EFFECTIVE HYPOVOLEMIA
- ↑ VP
- ↑ RENIN-ANGIOTESIN ALDOSTERONE
- H2O retention
- Water retention $>$ Na retention $=$ Hyponatremia
**Case-continued**

- Patient undergoes another LVP + i.v. albumin. Diuretics are held for a day and then restarted at a lower dose. Patient is counseled about Na restriction. He is discharged but returns in 7 days with tense ascites and fever, altered ms, and shortness of breath.
  - Pulse= 90/min
  - BP: 90/50
  - Bilirubin: 9 mg/dl
  - Creatinine: 3.5 mg/dl
  - 3 out of 3 blood cultures are positive for enterococci

**Type and Frequency of Injury in Acute Renal Failure in Cirrhosis**

<table>
<thead>
<tr>
<th>Type</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATN (ischemic)</td>
<td>Common</td>
</tr>
<tr>
<td>Prerenal failure</td>
<td></td>
</tr>
<tr>
<td>Decreased volume</td>
<td>Very common</td>
</tr>
<tr>
<td>HRS</td>
<td>Relatively common</td>
</tr>
<tr>
<td>Drugs</td>
<td>Relatively common</td>
</tr>
<tr>
<td>Obstruction</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Intrinsic</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>
Most infections are associated with complications of cirrhosis

N= 207 infections

Most infections are related to contact with health care system

N= 207 infections

Bajaj et al, Hepatology, 2012, Epub
Types of infection (first infection)

<table>
<thead>
<tr>
<th>Organism</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram positive</td>
<td></td>
</tr>
<tr>
<td>Streptococci</td>
<td>35</td>
</tr>
<tr>
<td>Methicillin-sensitive Staph</td>
<td>26</td>
</tr>
<tr>
<td>MRSA</td>
<td>17</td>
</tr>
<tr>
<td>Enterococcus</td>
<td>10</td>
</tr>
<tr>
<td>Vancomycin-resistant Enterococcus</td>
<td>26</td>
</tr>
<tr>
<td>Clostridium difficile</td>
<td>14</td>
</tr>
<tr>
<td>Gram negative</td>
<td></td>
</tr>
<tr>
<td>E Coli with</td>
<td>29</td>
</tr>
<tr>
<td>- extended beta lactamase resistance</td>
<td>49</td>
</tr>
<tr>
<td>- fluoroquinolone resistance</td>
<td>21</td>
</tr>
<tr>
<td>Klebsiella</td>
<td>24</td>
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<tr>
<td>Enterobacter</td>
<td>7</td>
</tr>
<tr>
<td>Others</td>
<td>6</td>
</tr>
<tr>
<td>Fungus (Candida)</td>
<td>13</td>
</tr>
</tbody>
</table>

Organisms associated with infections

Bajaj et al, Hepatology, 2012, Epub
Second infections have a different profile compared to first infection

(time median duration between first and second infection= 5 days)

- N= 207
- Aspiration: 28%
- Catheter UTI: 26%
- C Diff: 12%

Mortality is linked to type of infection, MELD score and second infections

- MRSA or VRE did not affect mortality
- Factors affecting outcome:
  - MELD
  - Second infection
  - Albumin

All infections are not equal in terms of effect on mortality
Impact of Enterococci on outcomes of SBP

- Enterococcus in neutrocytic ascites:
  - China: 4%
  - S Korea 7-19%
  - France 11-35%
  - USA 35%
  - Greece 38%
- Enterococcus seen in 50% Gm-positive SBP and 70% nosocomial SBP

Reuken et al, Alimentary Pharmacol and Ther, 2012; 35:1199-1200

Hepatorenal syndrome

- Cirrhosis with ascites
- Serum creatinine > 1.5 mg/dl
- No improvement after at least 2 days of diuretic withdrawal and volume replacement with albumin
- No nephrotoxic drugs used
- Absence of intrinsic renal disease

Reversal of HRS

Transplant-Free Survival

Overall survival 60 day: 48% (Terli) vs 46% (Placebo)

Sanyal et al, Gastroenterol, 2008
Impact of Reversal of HRS on Transplant-Free Survival

What is the best way to optimize medical treatment of HRS
How to optimize vasoconstrictor therapy

Concept # 1: Use albumin simultaneously


Concept # 2: Start Rx early because response rates drop as creatinine rises

Sanyal et al, Gastroenterology 2008
Boyer et al, J Hepatol, 2010
Failure of vasoconstrictors in those with multiple negative predictors

- Age >65 yrs
- Bili >6 mg/dl
- Failure to improve on albumin

Salerno et al, J Hep 2011

Concept #3: MAP response is linked to treatment response

Boyer et al, J Hepatol, 2010
How to optimize treatment with vasoconstrictors

- Start treatment early in the course of HRS
- Administer albumin simultaneously
- Treat for 72 hours before considering treatment failure unless multi-organ failure develops
- For partial responders, consider dose escalation
- Monitor MAP trends over the first 24-48 hrs and consideration dose escalation if adequate MAP response not seen

Stopping rules

- **Factors associated with treatment failure:**
  - Baseline creatinine >6 mg/dl
  - Failure to drop creatinine by 33% by 72 hr
  - Ventilator support due to multi-organ dysfunction

*Sanyal et al, Gastroenterology, 2008*
Once HRS resolves, how to keep it from recurring?

Long-term midodrine does not prevent recurrence of HRS

Allesandria et al, *Digestive and Liver Disease* 41 (2009)
Use of terlipressin on a continuous manner as a bridge to transplant for recurrent HRS

Can “transplant outcomes” be improved?
OLT and SLK survival 5/99-1/05

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>1 yr (%)</th>
<th>3 yr (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>OLT creat &gt;2</td>
<td>2190</td>
<td>79.7%</td>
<td>69.8%</td>
<td>.177</td>
</tr>
<tr>
<td>SLK creat &gt;2</td>
<td>208</td>
<td>86.1%</td>
<td>69.9%</td>
<td></td>
</tr>
<tr>
<td>OLT on RRT</td>
<td>1103</td>
<td>75.2%</td>
<td>68.3%</td>
<td>.0003</td>
</tr>
<tr>
<td>SLK on RRT</td>
<td>632</td>
<td>83.6%</td>
<td>74.8%</td>
<td></td>
</tr>
</tbody>
</table>

OLT = orthotopic liver transplantation
RRT = renal replacement therapy
SLK = simultaneous liver kidney transplantation

Gonwa et al. AJT 2006; 6: 2651-2659

SLK in the US 1993 - 2010


Source: www.unos.org
Indications for liver-kidney transplant

- AKI or HRS with creatinine >2 mg and requirement for RRT >8 weeks
- Cirrhosis with liver failure and CKD and >30% glomerulosclerosis or interstitial fibrosis

Eason et al, Am J Transplantation, 2008; 8:2243-2251