Hepatorenal Syndrome

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Clinical Case

- 66 year old woman
- Chronic Hepatitis C Virus induced cirrhosis
  - ascites
  - hepatic encephalopathy
  - initially uninterested in liver transplant
    - as she became sicker, decided to proceed
  - noted to be markedly jaundiced in clinic
  - admitted to the hospital for jaundice, failure to thrive
# Clinical Case

<table>
<thead>
<tr>
<th></th>
<th>Feb 2013</th>
<th>May 2013</th>
<th>July 2013 Admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>4.6</td>
<td>4.3</td>
<td>4.2</td>
</tr>
<tr>
<td>AST</td>
<td>255</td>
<td>224</td>
<td>94</td>
</tr>
<tr>
<td>ALT</td>
<td>150</td>
<td>151</td>
<td>69</td>
</tr>
<tr>
<td>GGT</td>
<td>31</td>
<td>26</td>
<td>21</td>
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<tr>
<td>Alk Phos</td>
<td>130</td>
<td>164</td>
<td>166</td>
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<tr>
<td>Total Bilirubin</td>
<td>9.1</td>
<td>11.2</td>
<td>32.1</td>
</tr>
<tr>
<td>Direct Bilirubin</td>
<td>3.6</td>
<td>--</td>
<td>20.0</td>
</tr>
<tr>
<td>INR</td>
<td>1.3</td>
<td>1.4</td>
<td>2.0</td>
</tr>
<tr>
<td>H / H</td>
<td>11.0 / 31.6</td>
<td>10.6 / 30.8</td>
<td>7.8 / 21.3</td>
</tr>
<tr>
<td>Sodium</td>
<td>131</td>
<td>130</td>
<td>122</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.67</td>
<td>0.69</td>
<td>0.69</td>
</tr>
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</table>
Clinical Case – creatinine

<table>
<thead>
<tr>
<th>HD1</th>
<th>HD2</th>
<th>HD3</th>
<th>HD4</th>
<th>HD5</th>
<th>HD6</th>
<th>HD7</th>
<th>HD8</th>
<th>HD9</th>
<th>HD10</th>
<th>HD11</th>
<th>HD12</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.69</td>
<td>0.73</td>
<td>0.65</td>
<td>0.55</td>
<td>0.54</td>
<td>0.61</td>
<td>0.98</td>
<td>1.44</td>
<td>1.80</td>
<td>2.72</td>
<td>3.32</td>
<td>3.82</td>
</tr>
</tbody>
</table>

- diuretics held due to low Na; pRBCs given for anemia
- NPO + IVF prep for colonoscopy
- diuretics restarted (ascites)
- diuretics stopped
- IV Fluids x >2 L
- CRRT recommended
- Family declined
- expiring

Other Studies:
- urine protein 93 mg/day
- urine RBC 0-3 / hpf
- renal ultrasound: no obstruction
- cultures negative
- no improvement with IVF
Renal Failure in Cirrhosis

**Causes**

- **Hypovolemia**
  - vomiting
  - diarrhea
  - gastrointestinal bleeding
  - diuretics

- **Drug-Induced**
  - NSAIDs
  - Aminoglycosides
  - ACE-inhibitors; ARBs

- **Intrinsic Renal Diseases** – ~15% of renal failure in cirrhosis
  - glomerulopathies
    - i.e., viral, alcohol
  - diabetes
  - hypertension

- **Systemic and Splanchnic Arterial Vasodilation**
  - Hepatorenal syndrome

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Cardenas *Clin Gastro Hep* 2009; 7:1287
Arroyo *Gastroenterology* 2002; 122:1658
Arroyo *Hepatology* 1996; 23:164
Renal Failure in Cirrhosis

**Initial Evaluation**
- **History/Exam/Studies:**
  - infection / sepsis
  - NSAIDs
  - high doses of diuretics or other drugs
  - GI fluid losses / bleeding
  - diabetes
  - arterial hypertension
  - urinary obstruction

**Laboratory Data:**
- Routine blood work
- urinalysis
- urine electrolytes / sediment
- 24-h urine volume, sodium, protein
- cultures of ascites, blood, and urine

**Radiology**
- renal ultrasound
  - r/o CKD or obstructive uropathy
- Chest X-ray
  - r/o pneumonia or effusion

Cardenas *Clin Gastro Hep* 2009; 7:1287
Hepatorenal Syndrome - Diagnosis

- Advanced liver failure (portal hypertension)
  - usually with ascites

- Low glomerular filtration rate
  - serum creatinine >1.5 mg/dL but <2.5 mg/dL - OR -
  - 24-hour CrCl (GFR) <40 mL/min

- Urine
  - < 500 mg/dL proteinuria
  - <50 RBC hematuria

- No ultrasound evidence of
  - obstructive uropathy
  - parenchymal renal disease

Arroyo *Gastroenterology* 2002;122:1658
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Cardenas *Clin Gastro Hep* 2009; 7:1287
Hepatorenal Syndrome - Diagnosis

- Additional minor criteria
  - Urine Volume <500 mL/day
  - Serum Na <130 mEq/L
  - Urine Na <10 mEq/L
  - Uosm > Posm

- Absence of:
  - shock
  - ongoing bacterial infection
  - recent nephrotoxic drugs
  - massive GI or renal fluid losses
  - massive GI or renal fluid losses

- no improvement (Cr <1.5 mg/dL) with at least 2 days of diuretic withdrawal and volume expansion
  - saline with albumin (1 g/kg body weight to maximum 100 g/d)

Cardenas *Clin Gastro Hep* 2009; 7:1287

Arroyo *Gastroenterology* 2002;122:1658
Arroyo *Hepatology* 1996; 23:164
Portal Hypertension

CIRRHOSIS

Early

STELLATE CELL ACTIVATION

S.C. CONTRACTION & PERISINUSOIDAL FIBROSIS

↑ INTRAHEPATIC VASCULAR RESISTANCE

PORTAL HYPERTENSION

Late

BACTERIAL OVERGROWTH & ↑ GUT CAPILLARY PERMEABILITY

↑ TRANSLOCATION FROM GUT OF BACTERIA & ENDOTOXINS

↓ PORTAL NO SYNTHESIS ↑ ENDOTHELIN RELEASE ↑ ET RECEPTORS

↑ SPLANCHNIC BLOOD FLOW AND VOLUME

↑ SPLANCHNIC & SYSTEMIC NO SYNTHESIS

SPLANCHNIC > SYSTEMIC VASODILATION; HYPERDYNAMIC CIRCULATION

SYSTEMIC HYPOTENSION
Pathophysiologic Mechanisms HRS

1. ↑ Renal sodium retention
2. ↑ Capacity to excrete solute free water
3. Hyponatremia
4. ↑ GFR

- Atrial natriuretic peptide
- Cardiac dysfunction
- ↑ Renal VD
- ↑ Renal VC
- ↑ RAAS
- ↑ SNS
- Baroreceptor activation
- Renal vessels
- Vasopressin release
- ↑ Effective circulating volume
- Portal hypertension
- Splanchnic vasodilation
- ↑ NO
- Liver
- Kidney
- Heart
- Brain
- Tachycardia

Wadei H M et al. CJASN 2006;1:1066-1079
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The Arterioles
Hepatorenal Syndrome

- Incidence
  - 24% in 5 years

- Increased risk if
  - Sodium <133
  - Plasma renin activity <3.5

Type I HRS
- develops in < 2 weeks
  - doubling of initial Cr to >2.5 mg/dL or
  - 50% reduction in initial CrCl to <20 mL/min
- median survival 2 weeks

Type II HRS
- slowly progressive course
  - creatinine usually 1.5 to 2.5 mg/dL
- median survival 6 months

NOTE – Type II can become Type I from either spontaneous progress or precipitating factors (i.e., infection)

Gines Gastro 1993; 105:229
Cardenas Clin Gastro Hep 2009; 7:1287
Arroyo Hepatology 1996; 23:164
Hepatorenal Syndrome - Treatment

Overall

Systemic Vasoconstrictors

- terlipressin
- \( \alpha \)-adrenergic agonists
  - midodrine
  - noradrenaline

NOTE: benefits of concomitant albumin have not been assessed in randomized studies.

Runyon *Hepatology* 2004; 39:841
Wong *Hepatology* 2004; 40:55
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Duvuox *Hepatology* 2002; 36:374
Moreau *Gastro* 2002; 122:923
Angeli *Hepatology* 1999; 29:1690
Guevara *Hepatology* 1998; 28:416
Hepatorenal Syndrome - Treatment

- For Type II HRS
  - Minimize nephrotoxins
  - Prevent progression to Type I HRS
    - SBP prophylaxis
    - SBP treatment – in addition to antibiotics
      - albumin 1.5 g/kg at diagnosis and 1 g/kg 48 hours later
- Liver Transplantation
  - post-OLT long-term survival decreased (60% at 3 years)

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Hepatorenal Syndrome - Treatment

For Type I

- randomized trial
  - Terlipressin/albumin – 40% improved
    - 1 mg Q4-6 hrs

- non-randomized trials
  - Terlipressin/albumin – 60-75% improved
  - Albumin / midodrine / octreotide
    - midodrine 2.5 mg TID to maximum of 12.5 mg TID
    - octreotide 100-200 μg subQ TID (or 25 μg/hr)
Hepatorenal Syndrome - Treatment

For Type I

- non-randomized controlled trials
  - Albumin / norepinephrine – 83% improved
    - norepinephrine 0.5-3 mg/h for up to 15 days
  - TIPS
    - limited application

- Hemodialysis
  - as bridge to transplantation

- Liver Transplantation

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It's QUESTION TIME!!