Management of hepatorenal syndrome

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Definitions of kidney injury in cirrhosis

*Acute Kidney Injury Network*

- **AKI**
  - A rise of serum creatinine of 50% above baseline
  - A rise of 0.3 mg/ml per day in less than 48 hours
- **CKD**
  - eGFR less than 60 ml/min for more than 3 months
- **Acute on CKD**
  - A rise of serum creatinine of 50% above baseline
  - A rise of 0.3 mg/ml per day in less than 48 hours in a person with CKD
Causes of AKI in cirrhosis

- Prerenal azotemia: the most common (45%)
- Intrarenal (structural kidney disease):
  - ATN
  - Glomerulopathies
- Obstructive uropathy
- HRS (23%)
  - Møller et al, Liver International 2014 Sep;34(8):1153-63
HRS: definition

- Progressive, functional, reversible, oliguric renal failure in cirrhosis or acute hepatic failure
- Absence of other triggers of renal disease
- Lack of response to volume expansion and withdrawal of diuretics over 2 days
## Stages of AKI

<table>
<thead>
<tr>
<th>Stage</th>
<th>Change in serum level of creatinine</th>
<th>Urine output</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>Increase of $\geq 26.4 \mu mol/L$ or 150%–200% from baseline</td>
<td>$&lt; 0.5 \text{ mL/kg hourly for } &gt; 6 \text{ h}$</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Increase $&gt; 200%–300%$ from baseline</td>
<td>$&lt; 0.5 \text{ mL/kg hourly for } &gt; 12 \text{ h}$</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Increase $&gt; 300%$ from baseline or $\geq 354 \mu mol/L$ with an acute increase of $\geq 44 \mu mol/L$</td>
<td>$&lt; 0.3 \text{ mL/kg hourly for } &gt; 24 \text{ h}$ or anuria for $&gt; 12 \text{ h}$</td>
</tr>
</tbody>
</table>
Survival is directly related to stage of AKI.
Survival is directly related to type of AKI
Fagundes C et al, J Hepatol, 2013
A prospective study of 192 patients with cirrhosis and AKI
Progression of AKI is an independent predictor of mortality

![Bar chart showing mortality rates across different stages of AKI and dialysis.]
Criteria for diagnosis of HRS
EASL guidelines 2010

- Cirrhosis with ascites
- Serum creatinine >133 μmol/l (1.5 mg/dl)
- No improvement of serum creatinine (decrease to a level of ≤133 μmol/l) after at least two days of diuretic withdrawal and volume expansion with albumin
- The recommended dose of albumin is 1 g/kg body weight per day up to a maximum of 100 g/day
- Absence of shock
- No current or recent treatment with nephrotoxic drugs
- Absence of parenchymal kidney disease as indicated by proteinuria >500 mg/ day, microhematuria (>50 red blood cells per high power field) and/or abnormal renal ultrasonography
TYPES OF HRS

• **HRS TYPE 1**
  - Cr>2.5 mg/dl or GFR<20 ml/min within 2 weeks
  - Acute decrease in GFR
  - Precipitating event
  - Grave prognosis
  - Associated with multiorgan failure

• **HRS TYPE 2**
  - Cr>1.5 mg/dl or GFR<40 ml/min
  - Chronic decrease in GFR
  - Spontaneous
  - Associated with refractory ascites
  - Better prognosis
AKI and HRS are common

- AKI occurs in 20% of hospitalized patients with cirrhosis
- HRS occurs in 39% of cirrhotics 5 years after the appearance of ascites
Precipitating factors of AKI and HRS are the same

- Large volume paracentesis
- Increased diuretic use
- SBP and other infections
- IV contrast
- GIB
Hepatorenal syndrome is invariably associated with ascites and extreme circulatory dysfunction.
Pathophysiology of ascites and hepatorenal syndrome

Progression of liver failure and portal hypertension

Increase in splanchnic arterial vasodilation

Decrease in cardiac output

Reduction in effective arterial blood volume

Moderate

Sodium retention

Severe

Water retention

Hyponatremia

Extreme

Type-2 Hepatorenal syndrome
Hypotension due to:
- Arterial vasodilation
- Reduced cardiac output

Portal hypertension

Activation of SNS, RAAS, AVP, endothelin and neuropeptide Y

Reduced sensitivity to NO and ANP

Increased local production of LTC₄, LTD₄ and F₂ isoprostane

\[ \downarrow \text{renal production of PGI₂ and PGE₂} \]

HRS
Factors that reduce renal blood flow precipitate or aggravate HRS

- Cardiac chronotropic and ionotropic incompetence (cirrhotic cardiomyopathy)
  – Should B-blockers be discontinued in advanced cirrhosis?
- Relative adrenal insufficiency with impaired ACTH and CRH release
- Infections, particularly SBP, which aggravate splanchnic vasodilatation
## Typical Urinary Findings in Renal Failure in Patients with Ascites

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Osmolarity (mosm/kg)</th>
<th>Urine (Na) (mmol/L)</th>
<th>Sediment</th>
<th>Protein mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prerenal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypovolemia</td>
<td>&gt;500</td>
<td>&lt;20</td>
<td>Normal</td>
<td>&lt;500</td>
</tr>
<tr>
<td>Hepatorenal syndrome</td>
<td>&gt;500</td>
<td>&lt;10</td>
<td>Normal</td>
<td>&lt;500</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute tubular necrosis</td>
<td>&lt;350</td>
<td>&gt;40</td>
<td>Granular Casts</td>
<td>500-1500</td>
</tr>
<tr>
<td>Interstitial nephritis</td>
<td>Variable</td>
<td>Variable</td>
<td>WBC eosinophils</td>
<td>500-1500</td>
</tr>
<tr>
<td>Glomerular disease</td>
<td>Variable</td>
<td>Variable</td>
<td>Red cell casts</td>
<td>Often &gt;1500</td>
</tr>
</tbody>
</table>
Treatment of AKI in cirrhosis

• Stop ACE and NSAIDs
• Stop diuretics
• Do large volume paracentesis
  – Reduces pressure on the IVC and improves cardiac output
  – Reduces pressure on the renal veins
Treatment of HRS

• Fluid challenge over 2 days
  – Albumin at 1 g/Kg/day, with a maximum of 100 g/day

• Correction and treatment of triggering factors

• Vasoconstrictors
  – Terlipressin
  – Midodrine
  – norepinephrine
Terlipressin for HRS
EASL practice guidelines, 2010

• Start at 0.5-1mg every 4-6 hours IV
• Increase to 2 mg every 4-6 hours IV if no improvement in 3 days
• Albumin at 1g/Kg on day 1 followed by 40 g/day
• Reversal of HRS occurs in 40-50% of patients
• Improved survival
  – RR 0.76 [95% confidence interval (CI) 0.61-0.95]
  – Survival improves in patients whose HRS is reversed
• Main side effect is ischemia
Midodrine

- Midodrine (up to 12.5 mo tid) plus albumin (10-20 g/day) plus octreotide 100 microgram tid or 25 microgram/hour
  - Reversal of HRS in majority of patients in three small studies
Norepinephrine

• 0.5 mg/hour IV and increased to achieve a 10 mm Hg increase in MAP
  – In a study on NE plus albumin plus furosemide, reversal of HRS in 83% of patients
  – Ischemic complications in 17%
Terlipressin Plus Albumin Versus Midodrine and Octreotide Plus Albumin in the Treatment of Hepatorenal Syndrome: A Randomized Trial

Terlipressin is superior in terms of partial and full response.
Only terlipressin use was associated with improved survival.
Terlipressin versus Norepinephrine in the Treatment of Hepatorenal Syndrome: A Systematic Review and Meta-Analysis

Reversal of HRS was similar in the two groups
Mortality rates at 30 days were similar.
Adverse events were lower with NE
HRS management summary

• Avoid AKI of any type in cirrhosis as it might progress to HRS
• Recognize and treat infections promptly
• Administer albumin when doing LVP
• Discontinue ACE, NSAIDs and diuretics
• Consider discontinuing B blockers
• Challenge your patient with AKI with albumin
• Administer a vasoconstrictor
Thank you