Acute Kidney Injury and Hepatorenal Syndrome in Patients with Cirrhosis

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RELATIONSHIP BETWEEN SERUM CREATININE & GFR IN PATIENTS WITH CIRRHOSIS

Inker, Perrone. Uptodate 2019 Online

OUTLINE

- Definition and staging of AKI in cirrhosis
- Differential diagnosis of AKI and role of kidney biomarkers
- Important issues on treatment of HRS
- In search of an algorithm for differential diagnosis and management of AKI in cirrhosis
RELATIONSHIP SERUM CREATININE & GFR IN PATIENTS WITH CIRRHOSIS

A serum creatinine of 1.5 g/dL corresponds to GFR of ~ 30 ml/min

Traditional criteria (IAC criteria)
50% percent increase of serum creatinine over baseline

Cut-off value of serum creatinine: 1.5 mg/dl (133µmol/l)

International Ascites Club-
Arroyo V et al, Hepatology. 1996

Gines P, Cárdenas Schrier’s Diseases of the Kidney 2013
1. Definition AKI:
Increase in sCr $\geq 0.3$ mg/dL ($\geq 26.5$ mmol/L) within 48 h; or a percent increase sCr $\geq 50\%$ from baseline which is known, or presumed, to have occurred within prior 7 days

2. Staging of AKI:

<table>
<thead>
<tr>
<th>Stage AKI</th>
<th>CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage 1</strong></td>
<td>increase in sCr $\geq 0.3$ mg/dL (26.5 mmol/L) or an increase in sCr $\geq 1.5$-fold to twofold from baseline</td>
</tr>
<tr>
<td>Stage 2</td>
<td>increase in sCr &gt;two to threefold from baseline</td>
</tr>
<tr>
<td>Stage 3</td>
<td>increase of sCr &gt;threefold from baseline or sCr $\geq 4.0$ mg/dL (353.6 mmol/L) with an acute increase $\geq 0.3$ mg/dL (26.5 mmol/L) or initiation of renal replacement therapy</td>
</tr>
</tbody>
</table>

*International Club of Ascites (ICA-AKI) definition*

EASL. J Hepatol 2018
# Prevalence and Causes of AKI in Patients With Cirrhosis

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>AKI Prevalence, %</th>
<th>Hypovolemia, %</th>
<th>ATN, %</th>
<th>HRS, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fagundes, et al. 2013</td>
<td>375</td>
<td>47</td>
<td>35</td>
<td>ND</td>
<td>18</td>
</tr>
<tr>
<td>Piano, et al. 2013</td>
<td>233</td>
<td>27</td>
<td>36</td>
<td>ND</td>
<td>43</td>
</tr>
<tr>
<td>Belcher, et al. 2014</td>
<td>110</td>
<td>ND</td>
<td>50</td>
<td>35</td>
<td>15</td>
</tr>
<tr>
<td>Alegretti, et al. 2015</td>
<td>120</td>
<td>ND</td>
<td>33</td>
<td>29</td>
<td>30</td>
</tr>
<tr>
<td>Tandon, et al. 2017</td>
<td>4733</td>
<td>36</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Huelin, et al. 2017</td>
<td>547</td>
<td>53</td>
<td>27</td>
<td>14</td>
<td>32</td>
</tr>
</tbody>
</table>

AKI & CIRRHOSIS

- AKI diagnosed with AKIN criteria has been shown to be associated with increased mortality in patients with cirrhosis.
- Progression through stages strongly correlates with an increased mortality in these patients.
- However, the cut-off of 1.5 mg/dl is still accurate.
- This cut-off identifies patients at risk.

Belcher et al., Hepatology 2013
Fagundes J Hepatol 2013
Wong, Angeli. J Hepatol 2016
Piano et al., Liv Int 2017
Serum Creatinine

**PROS**
- Easily obtainable
- Inexpensive
- Repeated measurements seem to be reliable
- Included in MELD score

**CONS**
- Overestimates GFR
  - Decreased creatine
  - Low muscle mass
  - Poor protein diet
  - High urine secretion
- Low sensibility
- Interlaboratory variability

Piano et al *Liv Int*. 2017
AKI IN CIRRHOSIS
Clinical relevance of the peak value of serum creatinine

A

\[
\begin{align*}
\text{sCR} < 1.5 \text{ mg/dl} & \quad \text{sCR} \geq 1.5 \text{ mg/dl} \\
\end{align*}
\]

Progression (%)

\[p < 0.01\]

B

\[
\begin{align*}
\text{sCR} < 1.5 \text{ mg/dl} & \quad \text{sCR} \geq 1.5 \text{ mg/dl} \\
\end{align*}
\]

Resolution (%)

\[p < 0.025\]

Piano et al. JHepatol 2013
ASSESSMENT OF AKI CLASSIFICATION IN CIRRHOSIS
Prospective studies in nonselected hospitalized patients

AKI 1A: peak creatinine ≤ 1.5 mg/dL
AKI 1B: peak creatinine > 1.5 mg/dL

Fagundes al J Hepatol 2013

Piano et al J Hepatol 2013
# NEW CATEGORIZATION OF AKI-STAGE 1

Serum creatinine value at diagnosis of AKI

<table>
<thead>
<tr>
<th></th>
<th>AKI-1A (S.Cr &lt; 1.5mg/dl)</th>
<th>AKI-1B (S.Cr ≥ 1.5mg/dl)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency (out of all AKI cases)</td>
<td>32 %</td>
<td>45 %</td>
<td></td>
</tr>
<tr>
<td>AKI resolution</td>
<td>75 %</td>
<td>50 %</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>AKI progression</td>
<td>13 %</td>
<td>38 %</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Associated ACLF</td>
<td>22 %</td>
<td>75 %</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>3-month mortality</td>
<td>29 %</td>
<td>57 %</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Huelin and Piano et al, Clin Gastroenterol Hepatol 2016
AKI DEFINITION AND STAGING IN CIRRHOSIS

The new diagnostic criteria of AKI in cirrhosis are helpful for early detection of acute impairment in kidney function.

The staging criteria of AKI should be modified and patients with stage 1 categorized into two groups, 1A and 1B according to a cut-off value of 1.5 mg/dL of serum creatinine at diagnosis of AKI.
Pathogenic mechanisms of acute kidney injury (AKI)

- Systemic hemodynamics
- Systemic inflammation/immune dysfunction
- Bacterial infection
- Volume loss secondary to gastrointestinal bleed, diuretics, diarrhea, large volume paracentesis
- Bile cast nephropathy
- Nephrotoxicity/tubular damage

*Maiwall et al. Hepatol Int 2016 Mar;10(2):245-57*
Main causes of acute kidney injury in cirrhosis

320 episodes of AKI (214 patients)

- **Prerenal**: 48% (154)
- **AKI-HRS**: 29% (93)
- **ATN**: 12% (39)
- **Other**: 11% (35)

*Huelin P et al. Hepatology 2019 In press*
MAIN TYPES OF AKI IN CIRRHOSIS

- **AKI-HEPATORENAL SYNDROME.**
  - Associated with and without bacterial infections.

- **HYPOVOLEMIA** *(diuretics, GI bleeding, diarrhea).*

- **ACUTE TUBULAR NECROSIS** *(shock, nephrotoxic drugs, other).*

- **NEPHROTOXICITY** *(NSAIDs)*

- **MISCELLANEOUS/UNKNOWN**

_Graupera I, Cardenas A. Clinical Liver Disease 2013_
DIFFERENTIAL DIAGNOSIS OF AKI IN CIRRHOSIS

• HEPATORENAL SYNDROME.
  – Associated with bacterial infections.
  – Without bacterial infections.

• HYPOVOLEMIA (diuretics, GI bleeding, diarrhea).

• ACUTE TUBULAR NECROSIS (shock, nephrotoxic drugs, other).

• NEPHROTOXICITY (NSAIDs)

• MISCELLANEOUS/UNKNOWN

- MEDICAL HISTORY
- PHYSICAL EXAMINATION
- BLOOD TESTS-
- URINE TESTS-
- ABDOMINAL US

Graupera I, Cardenas A. Clinical Liver Disease 2013
Conventional Markers of AKI

- Fractional excretion of filtered sodium ($\text{FE}_{\text{Na}}$)
  - May be artificially increased by diuretics
  - Low in acute GN, AIN, ATN with intact distal tubule function
  - Not independently associated with progression of AKI and mortality
  - Accuracy in identifying prerenal azotemia is poor

Neutrophil gelatinase-associated lipocalin (NGAL) – protein from lipocalin superfamily – Acute-phase reactant and may be released from neutrophils, macrophages, and other immune cells in response to inflammation or epithelial injury.

Adapted from Koyner et al, Clin J Am Soc Nephrol 2013
DIFFERENTIAL DIAGNOSIS OF AKI IN CIRRHOSIS

Role of uNGAL

Fagundes et al, J Hepatol 2012
### DIFFERENTIAL DIAGNOSIS OF AKI IN CIRRHOSIS

#### Usefulness of other urine biomarkers

<table>
<thead>
<tr>
<th></th>
<th>PRE-RENAL (N = 55)</th>
<th>HRS (N = 16)</th>
<th>ATN (N = 39)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGAL (ng/mL)</td>
<td>54 (17-180)</td>
<td>115 (51-373)</td>
<td>565 (76-1000)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IL-18 (pg/mL)</td>
<td>15 (15-49)</td>
<td>37 (15-90)</td>
<td>124 (15-325)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Albumin (mg/dL)</td>
<td>21 (4-70)</td>
<td>24 (13-129)</td>
<td>92 (44-253)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>KIM-1 (ng/mL)</td>
<td>4.4 (1.8-11.7)</td>
<td>7.6 (4.5-10.1)</td>
<td>8.4 (4.1-18.3)</td>
<td>0.03</td>
</tr>
<tr>
<td>L-FABP (ng/mL)</td>
<td>9 (4-18)</td>
<td>14 (6-20)</td>
<td>27 (8-103)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*Belcher et al, Hepatology 2014*
Urinary NGAL values in patients with cirrhosis and HRS and ATN

NGAL Cutoff- 220 ng/ML

P. Huelin et al. Hepatol. 2019 In press
## Urinary NGAL values in patients with cirrhosis and AKI

<table>
<thead>
<tr>
<th></th>
<th>Hypovolemia-induced</th>
<th>HRS-AKI</th>
<th>ATN</th>
<th>Miscellaneous</th>
<th>p</th>
<th>ATN vs other</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Continuous variable</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>AUROC (95%CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cut-Off Point$</td>
</tr>
<tr>
<td>Day 1 (all patients)*</td>
<td>153</td>
<td>93</td>
<td>39</td>
<td>35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NGAL (µg/g)</td>
<td>48 (22-97)</td>
<td>76 (18-177)</td>
<td>799 (153-2114)</td>
<td>317 (49-759)</td>
<td>&lt;0.001</td>
<td>0.80 (0.72-0.88)</td>
</tr>
<tr>
<td>mNGAL (µg/g)</td>
<td>33 (14-67)</td>
<td>44 (13-115)</td>
<td>543 (108-1838)</td>
<td>236 (41-570)</td>
<td>&lt;0.001</td>
<td>0.80 (0.72-0.88)</td>
</tr>
<tr>
<td>IL-18 (pg/g)</td>
<td>9 (3-21)</td>
<td>8 (1-26)</td>
<td>33 (11-107)</td>
<td>14 (3-53)</td>
<td>&lt;0.001</td>
<td>0.70 (0.60-0.79)</td>
</tr>
<tr>
<td>Day 3**</td>
<td>87</td>
<td>59</td>
<td>35</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NGAL (µg/g)</td>
<td>63 (37-92)</td>
<td>114 (49-149)</td>
<td>674 (317-2611)</td>
<td>246 (186-671)</td>
<td>&lt;0.001</td>
<td>0.87 (0.78-0.95)</td>
</tr>
<tr>
<td>mNGAL (µg/g)</td>
<td>32 (20-57)</td>
<td>66 (27-115)</td>
<td>293 (94-762)</td>
<td>188 (74-648)</td>
<td>&lt;0.001</td>
<td>0.80 (0.71-0.89)</td>
</tr>
<tr>
<td>IL-18 (pg/g)</td>
<td>4 (0-7)</td>
<td>5 (2-10)</td>
<td>9 (4-32)</td>
<td>7 (3-12)</td>
<td>0.006</td>
<td>0.66 (0.54-0.76)</td>
</tr>
</tbody>
</table>

Values of NGAL, mNGAL, and IL-18 are median (IQ ranges) and are expressed as µg or pg per gram of creatinine, respectively

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*P. Huelin et al. Hepatol. 2019 In press*
Rapid identification of the type of AKI is very important to start specific treatment.

Urine biomarkers, particularly NGAL and IL-18 are useful in the differential diagnosis between ATN vs HRS and other types of AKI in cirrhosis.

Cut off 220ng/mL
Management of AKI in Cirrhosis

1. Stop nephrotoxic drugs, vasodilators, (NSAIDs) and diuretics
2. Treat bacterial infections
3. Prerenal AKI – IV albumin
4. Rule out intrinsic AKI
5. HRS - volume expansion & vasconstrictors

HEPATORENAL SYNDROME
International Ascites Club - Diagnostic Criteria

1. Diagnosis of cirrhosis and ascites.
2. Meet AKI criteria
3. No response after 2 days with diuretic withdrawal and volume expansion with albumin (1 g/kg/day with max. of 100 g/day).
4. Absence of shock and recent use of nephrotoxic drugs.
5. No parenchymal kidney disease:
   - Proteinuria >500 mg/day, no microhematuria (>50Rbc) and/or abnormal renal ultrasound
Advanced cirrhosis

Portal hypertension

- Cirrhotic cardiomyopathy
  - Cardiac output
- Splanchnic arterial vasodilation
  - Decreased vascular resistance
  - Effective arterial hypovolaemia
    - Activation of vasoconstrictor factors: RAAS, SNS, AVP
    - Renal vasoconstriction
      - Decreased GFR

Impaired renal autoregulation

Prostaglandins

Kidney tissue injury?

Inflammatory response

- Inflammatory mediators and/or vasodilator factors (IL-6, TNF, endotoxin)
- Activation of immune cells
- DAMPs (HMGB1, HSPs and hyaluronic acid)

Albumin

Terlipressin/Noradrenaline
Management of HRS-AKI: treatment

- First-line therapy is terlipressin plus albumin*

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Grade of evidence</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients meeting the current definition of HRS-AKI stage &gt;1A should be expeditiously treated with <strong>vasoconstrictors and albumin</strong></td>
<td>III</td>
<td>1</td>
</tr>
<tr>
<td>Terlipressin can be administered by IV boluses (1 mg every 4–6 hours) or by continuous IV infusion (2 mg/day)† • In case of <strong>non-response</strong> (decrease in SCr &lt;25% from the peak value) after 2 days, the dose of <strong>terlipressin should be increased</strong> in a stepwise manner to a <strong>maximum of 12 mg/day</strong></td>
<td>I</td>
<td>1</td>
</tr>
<tr>
<td>Albumin solution (20%) should be used at 20–40 g/day • Serial measures assessing central blood volume can help to titrate the dose of albumin to prevent circulatory overload</td>
<td>II-2</td>
<td>1</td>
</tr>
<tr>
<td>Noradrenaline can be an alternative to terlipressin‡ • Requires a central venous line often in an ICU Midodrine + octreotide can be an option when terlipressin or noradrenaline are unavailable (but efficacy is much lower)</td>
<td>I</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>1</td>
</tr>
</tbody>
</table>

*EASL CPG decompensated cirrhosis. J Hepatol 2018; doi: 10.1016/j.jhep.2018.03.024*
HEPATORENAL SYNDROME
Treatment with terlipressin and albumin

**Diagnosis of HRS**

0 3 6 9 12 15 Days

Terlipressin, bolus i.v. 1 mg/4-6 h or continuous infusion

Albumin i.v. 1 g/Kg

Albumin 20-40 g/day

Increase terlipressin dose if creatinine does not decrease by 25% on day 3

*Solà E, Cárdenas A, Ginès P. Curr Opin Organ Transplant. 2013 Jun;18(3):265-70*
Terlipressin/albumin (n=27) vs midodrine and octreotide / albumin (n=22) for HRS

Terlipressin (continuous IV infusion)
Oct / Mido (subcutaneous / oral)

Cavallin et al., Hepatology 2016
Probability of 90-day transplant free survival according to response to treatment

Terlipressin/albumin (n=27) vs midodrine and octreotide / albumin (n=22) for HRS

Survival rate

Time (days)

Responders
Nonresponders
Meta-analysis of terlipressin efficacy to reduce mortality in patients with cirrhosis and hepatorenal syndrome

Terlipressin vs Noradrenaline in Patients With ACLF and HRS-AKI: Open-Label RCT (n=60 each arm)

Continuous IV infusion of terlipressin (2 to 12 mg/day) n = 60 vs noradrenaline (0.5 to 3 mg/hour) n = 60

Hepatorenal Syndrome

Evaluate for liver transplantation

Candidate

High priority for liver transplantation

Vasoconstrictors + Albumin

Response*

yes

Stop after complete response or until a maximum of 15 days

no

Consider renal replacement therapy

Not a candidate

Vasoconstrictors + Albumin

* case by case basis

No Response

Consider renal replacement therapy in selected cases

Cárdenas A, Gines P Gut 2011
MANAGEMENT OF AKI IN PATIENTS WITH CIRRHOSIS

SCr < 1.5

AKI-1A

Remove risk factors (withdrawal of nephrotoxic drugs, vasodilators and NSAIDs, decrease/withdrawal of diuretics, treatment of infections when diagnosed), plasma volume expansion in case of hypovolemia

Close monitoring

Resolution
Stable
Progression

Close follow-up

Futher treatment of AKI decided on a case-by-case basis

AKI 1B, 2 and 3

SCr > 1.5

Withdrawal of diuretics (if not withdrawn already) and volume expansion with albumin (1 g/kg) for 2 days

Response

YES

NO

Kidney biomarkers

Increased

Decreased

ACUTE TUBULAR NECROSIS

HEPATOORENAL SYNDROME

Ginès et al, Nat Rev Dis Primers. 2018 / EASL CPG 2018
Muchas gracias!