PERSPECTIVES IN THE MANAGEMENT OF RENAL DYSFUNCTION IN CIRRHOSIS

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OUTLINE

• Definition and staging of AKI in cirrhosis
• Differential diagnosis of AKI and role of kidney biomarkers
• Prognosis and relevance of type of AKI
• Important issues on treatment of type-1 HRS
• In search of an algorithm for differential diagnosis and management of AKI in cirrhosis
AGENDA

• Definition and staging of AKI in cirrhosis

• Differential diagnosis of AKI and role of kidney biomarkers

• Prognosis and relevance of type of AKI

• AKI due to non-steroidal anti-inflammatory drugs

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RELATIONSHIP SERUM CREATININE & GFR IN PATIENTS WITH CIRRHOSIS

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

<table>
<thead>
<tr>
<th>Creatinine (mg/dL)</th>
<th>GFR (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.7</td>
<td>104</td>
</tr>
<tr>
<td>1.0</td>
<td>70</td>
</tr>
<tr>
<td>2.0</td>
<td>20</td>
</tr>
<tr>
<td>2.3</td>
<td>13</td>
</tr>
</tbody>
</table>

Cárdenas et al. (unpublished)
1. Definitions used:

- **Traditional criteria (IAC criteria)**
  50% percent increase of serum creatinine over baseline
  Cut-off value of serum creatinine: 1.5 mg/dl (133µmol/l)

- **AKIN criteria**
  AKI (Acute Kidney Injury): ≥ 0.3 mg/dL or 50% in serum creatinine within 48 hours.
  No cut-off value
  Classification in stages of severity: 1, 2 and 3
  High sensitivity
  Detects impairment of kidney function with “normal” GFR

**Stage 1**  Increase in sCr ≥ 0.3 mg/dl or sCr (1.5- to 2-fold) from baseline
**Stage 2**  Increase in sCr >2-3 fold from baseline
**Stage 3**  Increase in sCr >3 fold from baseline or sCr ≥ 4mg/dl
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
AKI IN CIRRHOSIS
Clinical relevance of the peak value of serum creatinine

Piano et al. JHepatol 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 STAGING IN CIRRHOSIS

Take-home message

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.
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MAIN TYPES 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

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

• HEPATURENAL 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
MAIN URINE BIOMARKERS

GLOMERULUS
Creatinine
Albumin
NGAL

PROXIMAL TUBULE
NGAL
IL-18
KiM-1
L-FABP
MCP-1
Albumin

DISTAL TUBULE
NGAL
GST-π

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
<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
DIFFERENTIAL DIAGNOSIS BETWEEN HRS AND ATN
Role of Urine IL-18 and NGAL

IL-18

Area Under the ROC Curve (95% CI)

- Ahmed 2014: 0.98 [0.91, 1.00]
- Ariza 2015: 0.92 [0.84, 1.00]
- Belcher 2014: 0.71 [0.61, 0.81]
- Tsai 2013: 0.88 [0.81, 0.95]
- Pooled Estimate: 0.88 [0.79, 0.97]

NGAL

Area Under the ROC Curve (95% CI)

- Ahmed 2014: 0.91 [0.81, 0.97]
- Ariza 2015: 0.96 [0.89, 1.00]
- Belcher 2014: 0.78 [0.69, 0.88]
- Fagundes 2012: 0.82 [0.67, 0.97]
- Treprasertsuk 2015: 0.91 [0.83, 0.98]
- Pooled Estimate: 0.89 [0.84, 0.94]

Puthumana et al, Ciln Gastroenterol Hepatol 2017
Take-home message

There are a number of types of Acute kidney injury in cirrhosis. 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.
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• In search of an algorithm for differential diagnosis and management of AKI in cirrhosis
PROGNOSIS OF PATIENTS WITH CIRRHOSIS AND AKI

Relevance of the type of AKI

Take-home message

The type of AKI is a very important prognostic factor in patients with cirrhosis. Hepatorenal syndrome and ATN have the worst prognosis.
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• **Important issues on treatment of type-1 HRS**

• In search of an algorithm for differential diagnosis and management of AKI in cirrhosis
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 and/or abnormal renal ultrasound
CIRCULATORY AND KIDNEY FUNCTION IN HEPATORENAL SYNDROME AND EFFECTS OF TERLIPRESSIN AND ALBUMIN

CIRRHOSIS

\[ \text{Portal hypertension} \]

Terlipressin \rightarrow Splanchnic arterial vasodilation

Albumin \rightarrow Decreased effective arterial blood volume

Vasoconstrictor systems

Cerebral vasoconstriction

Renal vasoconstriction

Brachial/femoral vasoconstriction

Maintenance of effective arterial blood volume

HEPATORENAL SYNDROME
CIRCULATORY AND KIDNEY FUNCTION IN HEPATORENAL SYNDROME AND EFFECTS OF TERLIPRESSIN AND ALBUMIN

CIRRHOSIS

\[ \text{Portal hypertension} \]

\[ \text{Splanchnic arterial vasoconstriction} \]

\[ \text{Increase in effective arterial blood volume} \]

\[ \text{Suppressed vasoconstrictor systems} \]

\[ \begin{align*} \text{Cerebral vasodilation??} \\
\text{Kidney vasodilation} \\
\text{Brachial/femoral Vasodilation??} \\
\text{Maintenance of effective arterial blood volume} \end{align*} \]

IMPROVED KIDNEY FUNCTION
TYPE 1 HRS (SCr >2.5mg/dl). EFFECTS OF TERLIPRESSIN AND ALBUMIN

- Terlipressin * bolus or continuous infusion
- Increase terlipressin dose if creatinine does not decrease by 25% on day 3

Liver Transplantation

<table>
<thead>
<tr>
<th>Days</th>
<th>Pre-admission</th>
<th>Admission</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
<th>16</th>
<th>17</th>
<th>18</th>
<th>19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Creatinine (mg/dL)</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td>11</td>
<td>12</td>
<td>13</td>
<td>14</td>
<td>15</td>
<td>16</td>
<td>17</td>
<td>18</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>100</td>
<td>95</td>
<td>90</td>
<td>85</td>
<td>80</td>
<td>75</td>
<td>70</td>
<td>65</td>
<td>60</td>
<td>55</td>
<td>50</td>
<td>45</td>
<td>40</td>
<td>35</td>
<td>30</td>
<td>25</td>
<td>20</td>
<td>15</td>
<td>10</td>
</tr>
</tbody>
</table>

* uNGAL 186 µg/gr
* uNGAL 105 µg/gr

Albumin 1g/Kg
Terlipressin * 4-12 mg/day + Albumin 20-40g/day
Terlipressin/albumin (n=27) vs midodrine and octreotide / albumin (n=22) for HRS

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

70.4% partial
28.6% complete

P = 0.01
P < 0.001

Cavallin et al., Hepatology 2015
Systematic review with meta-analysis: vasoactive drugs for the treatment of hepatorenal syndrome type 1

HRS reversal

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Terlipressin</th>
<th>Placebo/no intervention</th>
<th>Risk ratio</th>
<th>Risk ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Boyer 2016</td>
<td>42</td>
<td>97</td>
<td>28</td>
<td>99</td>
</tr>
<tr>
<td>Martin-Llahi 2008</td>
<td>6</td>
<td>17</td>
<td>1</td>
<td>18</td>
</tr>
<tr>
<td>Neri 2008</td>
<td>21</td>
<td>26</td>
<td>5</td>
<td>26</td>
</tr>
<tr>
<td>Sanyal 2008</td>
<td>33</td>
<td>56</td>
<td>14</td>
<td>56</td>
</tr>
<tr>
<td>Solanki 2003 (1)</td>
<td>5</td>
<td>12</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>208</td>
<td>211</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>107</td>
<td>48</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 8.35, df = 4 (P = 0.08); I^2 = 52$
Test for overall effect: $Z = 3.52 (P = 0.0004)$

Footnotes
(1) Solanki – definition of HRS reversal not given
Type-1 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
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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

SCr > 1.5

AKI 1B, 2 and 3

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

Response

YES
NO

Kidney biomarkers

Increased
Decreased

ACUTE TUBULAR NECROSIS
HEPATORENAL SYNDROME

Ginès et al, 2016
Muchas gracias!
TREATMENT OF HEPATORENAL SYNDROME WITH TERLIPRESSIN AND ALBUMIN

Adverse cardiovascular effects (combined studies, 327 patients)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrhythmias</td>
<td>13</td>
<td>4%</td>
</tr>
<tr>
<td>Circulatory overload</td>
<td>11</td>
<td>3.4%</td>
</tr>
<tr>
<td>Peripheral ischemia</td>
<td>6</td>
<td>1.8%</td>
</tr>
<tr>
<td>Suspected intestinal ischemia</td>
<td>4</td>
<td>1.2%</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>3</td>
<td>0.9%</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2</td>
<td>0.6%</td>
</tr>
</tbody>
</table>
**TERLIPRESSIN AND ALBUMIN FOR HRS**

Adverse cardiovascular effects

<table>
<thead>
<tr>
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</tr>
<tr>
<td>Myocardial infarction</td>
<td>2</td>
<td>0.6%</td>
</tr>
<tr>
<td>Cause</td>
<td>Hypovolemia (n=62)</td>
<td>Infection (n=54)</td>
</tr>
<tr>
<td>----------------</td>
<td>---------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>AKI 1</td>
<td>56</td>
<td>36</td>
</tr>
<tr>
<td>AKI 2</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>AKI 3</td>
<td>3</td>
<td>10</td>
</tr>
</tbody>
</table>

*Fagundes et al. JHepatol 2013*
HEPATOURENAL SYNDROME
Treatment with terlipressin and albumin

Diagnosis of HRS

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
RELATIONSHIP BETWEEN SERUM CREATININE & GFR IN PATIENTS WITH CIRRHOSIS

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

Francoz, et al J Hepatol 2016
Piano et al Liv Int 2017
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NSAIDs-ASSOCIATED AKI IN CIRRHOSIS

Time course of serum creatinine according to AKI type

*Elia et al, J Hepatol 2015*
NSAIDs-ASSOCIATED AKI IN CIRRHOSIS

Survival according to AKI type

$p < 0.001$
NSAIDs-ASSOCIATED AKI IN CIRRHOSIS

Take-home message

_Treatment with NSAIDs should always be investigated in patients admitted to hospital with AKI. Contrary to current belief, kidney and patient outcomes are not always favorable. While kidney function recovers rapidly in two thirds of patients, one third of cases develop persistent AKI with high mortality._
<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Terlipressin Events</th>
<th>Terlipressin Total</th>
<th>Noradrenaline Events</th>
<th>Noradrenaline Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alessandria 2007</td>
<td>4</td>
<td>5</td>
<td>3</td>
<td>4</td>
<td>29.3%</td>
<td>1.07 [0.52, 2.18]</td>
<td></td>
</tr>
<tr>
<td>Sharma 2008</td>
<td>10</td>
<td>20</td>
<td>10</td>
<td>20</td>
<td>39.1%</td>
<td>1.00 [0.54, 1.86]</td>
<td></td>
</tr>
<tr>
<td>Singh 2012</td>
<td>9</td>
<td>23</td>
<td>10</td>
<td>23</td>
<td>31.5%</td>
<td>0.90 [0.45, 1.80]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>48</strong></td>
<td><strong>47</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td></td>
<td><strong>0.99 [0.67, 1.45]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 23

Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.13, df = 2 (P = 0.94); I^2 = 0%

Test for overall effect: Z = 0.07 (P = 0.94)
RENAL FAILURE IN CIRRHOSIS

- **Definition:** Impairment of glomerular filtration rate
  Acute renal failure in most cases
  Chronic renal failure less common

- **Frequency:**
  Up to 30% in hospitalized patients
  Very common in ICU patients

- **Predisposing factor:** Impairment of circulatory function

- **Causes:**
  Hepatorenal syndrome
  Bacterial infections
  Hypovolemia
  Nephrotoxicity
  Acute tubular necrosis (i-AKI)
  Chronic kidney diseases

- **Prognosis:** Associated with high mortality
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
ACUTE IMPAIRMENT OF KIDNEY FUNCTION IN CIRRHOSIS

International Club of Ascites (ICA-AKI) definition

1. Definition AKI:
Increase in sCr ≥0.3 mg/dL (≥26.5 mmol/L) within 48 h; or a percent increase sCr ≥50% from baseline which is known, or presumed, to have occurred within the prior 7 days

2. Staging of AKI:

<table>
<thead>
<tr>
<th>Stage AKI</th>
<th>CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>increase in sCr ≥0.3 mg/dL (26.5 mmol/L) or an increase in sCr ≥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 ≥4.0 mg/dL (353.6 mmol/L) with an acute increase ≥0.3 mg/dL (26.5 mmol/L) or initiation of renal replacement therapy</td>
</tr>
</tbody>
</table>
RENAL FAILURE IN CIRRHOSIS

Volume depletion?

Albumin infusion*

GI bleed
Shock

Acute Tubular Necrosis

Nephrotoxic drugs? (NSAIDs), other

NEPHROTOXICITY

Signs of infection?

Proteinuria and/or hematuria?

PARENCHYMAL NEPHROPATHY

Abnormal renal Ultrasonography?

Hepatorenal Syndrome

** HRS associated with infections

Physical exam & Laboratory data

History & physical exam

Renal ultrasonography

Graupera I, Cardenas A. Clinical Liver Disease 2013