Hepatorenal syndrome: Is it just AKI?

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DISCLOSURES

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- NIH/NIDDK U01 58369
  - US Acute Liver Failure Study Group (Co-PI)

Speakers Bureau

- Gambro
1. Describe the pathophysiological mechanisms contributing to hepatorenal syndrome and acute kidney injury (AKI) in cirrhosis.

2. Review updated clinical definitions of AKI in cirrhosis and examine the role of etiology of AKI on natural history of cirrhotic patients in the presence/absence of liver transplant (LT).

3. Examine the utility of traditional blood tests and novel biomarkers in assessing AKI in cirrhosis and in prognostication.

4. Review therapeutic interventions to manage and reverse hepatorenal syndrome (HRS-AKI) in cirrhosis.
Hepatorenal pathophysiology

Four related pathways initiated by hepatic decompensation:

1. Hyperdynamic circulation and ↓ PVR

2. Stimulation of neuro-hormonal compensation in the renal circulation (i.e., RAAS; SNS; ADH)

3. Cardiac dysfunction (cirrhotic cardiomyopathy) compounding circulatory derangements and kidney hypoperfusion

4. Inflammatory/vasoactive mediator induced direct renal injury and indirect effects on renal vascular circulation
HRS: Peripheral Arterial Vasodilatation Hypothesis

Renal Blood Flow in Cirrhosis

n=70 cirrhotic patients

↓ Renal BF before ascites, hyponatremia and AKI

Ring-Larsen et al Scand J Clin Lab Invest 1977
Traditional approach to AKI in Cirrhosis

**AKI**

(serum creatinine >1.5 mg/dL)

- Volume depletion or Vasodilators
  - **PRERENAL FAILURE**
    - Shock

- Nephrotoxic drugs (NSAIDs)
  - **NEPHROTOXICITY**
    - Active sediment, proteinuria and/or hematuria
    - Septic Shock

- Signs of infection
  - **PARENCHYMAL NEPHROPATHY**
    - Abnormal renal ultrasonography

- **HEPATORENAL SYNDROME**

*Ginès P et al., Lancet 2003*
Box 1. Diagnostic criteria of hepatorenal syndrome (HRS) type of acute kidney injury (AKI) in patients with cirrhosis

HRS-AKI

• Diagnosis of cirrhosis and ascites

• Diagnosis of AKI according to ICA-AKI criteria

• No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin 1 g per kg of body weight

• Absence of shock

• No current or recent use of nephrotoxic drugs (NSAIDs, aminoglycosides, iodinated contrast media, etc.)

• No macroscopic signs of structural kidney injury*, defined as:
  - absence of proteinuria (>500 mg/day)
  - absence of microhaematuria (>50 RBCs per high power field),
  - normal findings on renal ultrasonography

*Patients who fulfil these criteria may still have structural damage such as tubular damage. Urine biomarkers will become an important element in making a more accurate differential diagnosis between HRS and acute tubular necrosis.
ICA, International Club of Ascites; NSAIDs, non-steroidal anti-inflammatory drugs; RBCs, red blood cells.
# Diagnosis and management of acute kidney injury in patients with cirrhosis: Revised consensus recommendations of the International Club of Ascites

Paolo Angeli\(^1\),*, Pere Ginès\(^2\), Florence Wong\(^6\), Mauro Bernardi\(^7\), Thomas D. Boyer\(^8\), Alexander Gerbes\(^9\), Richard Moreau\(^10,11,12\), Rajiv Jalan\(^13\), Shiv K. Sarin\(^14\), Salvatore Piano\(^1\), Kevin Moore\(^15\), Samuel S. Lee\(^16\), Francois Durand\(^17,18\), Francesco Salerno\(^19\), Paolo Caraceni\(^7\), W. Ray Kim\(^20\), Vicente Arroyo\(^2,3,4\), Guadalupe Garcia-Tsao\(^21\)

<table>
<thead>
<tr>
<th>Subject</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline sCr</strong></td>
<td>A value of sCr obtained in the previous 3 months, when available, can be used as baseline sCr. In patients with more than one value within the previous 3 months, the value closest to the admission time to the hospital should be used. In patients without a previous sCr value, the sCr on admission should be used as baseline.</td>
</tr>
</tbody>
</table>
| **Definition of AKI** | • Increase in sCr ≥0.3 mg/dl (≥26.5 µmol/L) within 48 hours; or,  
  • A percentage increase sCr ≥50% from baseline which is known, or presumed, to have occurred within the prior 7 days |
| **Staging of AKI**    | • **Stage 1**: increase in sCr ≥0.3 mg/dl (26.5 µmol/L) or an increase in sCr ≥1.5-fold to 2-fold from baseline  
  • **Stage 2**: increase in sCr >2-fold to 3-fold from baseline  
  • **Stage 3**: increase of sCr >3-fold from baseline or sCr ≥4.0 mg/dl (353.6 µmol/L) with an acute increase ≥0.3 mg/dl (26.5 µmol/L) or initiation of renal replacement therapy |
| **Progression of AKI**| **Progression**  
  Progression of AKI to a higher stage and/or need for RRT  
  **Regression**  
  Regression of AKI to a lower stage |
| **Response to treatment** | **No response**  
  No regression of AKI  
  **Partial response**  
  Regression of AKI stage with a reduction of sCr to ≥0.3 mg/dl (26.5 µmol/L) above the baseline value  
  **Full response**  
  Return of sCr to a value within 0.3 mg/dl (26.5 µmol/L) of the baseline value |
<table>
<thead>
<tr>
<th></th>
<th>AKI Definition</th>
<th>AKI Stage Serum Creatinine Criteria</th>
<th>AKI Stage Urine Output Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RIFLE (2004)</strong></td>
<td>( \text{sCr} \geq 1.5 \times \text{baseline, within 7 d; or GFR} ) ( \uparrow &gt;25% ); or urine output (UO) &lt;0.5 mL/kg/h ( \times 6 \text{ h} )</td>
<td>( 1 ) (Risk) ( \geq 1.5 \times \text{baseline or GFR} ) ( \uparrow &gt;25% )</td>
<td>( 2 ) (Injury) ( \geq 2 \times \text{baseline or GFR} ) ( \uparrow &gt;50% )</td>
</tr>
<tr>
<td><strong>AKIN (2007)</strong></td>
<td>( \text{sCr} \geq 0.3 \text{ mg/dL} ) (26.5 \text{ µmol/L}) within 48 h; or ( \text{sCr} \geq 1.5 \times \text{baseline within 48 h; or UO} ) &lt;0.5 mL/kg/h ( \times 6 \text{ h} )</td>
<td>( \geq 0.3 \text{ mg/dL} ) (&gt;26.5 \text{ µmol/L}) within 48 h or ( \geq 1.5 \times \text{baseline} )</td>
<td>( 2-3 \times \text{baseline} )</td>
</tr>
<tr>
<td><strong>KDIGO (2012)</strong></td>
<td>( \text{sCr} \geq 0.3 \text{ mg/dL} ) (26.5 \text{ µmol/L}) within 48 h; or ( \text{sCr} \geq 1.5 \times \text{baseline, which is known or presumed to have occurred within the prior 7 d; or UO} ) &lt;0.5 mL/kg/h for 6 h</td>
<td>( \geq 0.3 \text{ mg/dL} ) (&gt;26.5 \text{ µmol/L}) within 48 h or ( \geq 1.5 \times \text{baseline} )</td>
<td>( 2-3 \times \text{baseline} )</td>
</tr>
<tr>
<td><strong>ADQI (2010)</strong></td>
<td>( \text{sCr} \geq 0.3 \text{ mg/dL} ) (26.5 \text{ µmol/L}) within 48 h; or ( \text{sCr} \geq 1.5 \times \text{baseline} ) ( \text{HRS-1 is a specific form of AKI} )</td>
<td>( \geq 0.3 \text{ mg/dL} ) (&gt;26.5 \text{ µmol/L}) within 48 h or ( \geq 1.5 \times \text{baseline} )</td>
<td>( 2-3 \times \text{baseline} )</td>
</tr>
</tbody>
</table>
| **AKI in cirrhosis** | **ICA (2015)** \( \text{sCr} \geq 0.3 \text{ mg/dL} \) (26.5 \text{ µmol/L}) within 48 h; or \( \text{sCr} 

Angeli et al, J Hepatol 2015
Karvellas et al, Crit Care Clin 2015
Cirrhosis-associated AKI

- >50% increase in Cr level baseline in <6 months
- increase of 0.3 mg/dL in <48 hours.
- 337 cirrhotics admitted with infection
  - 30-day mortality was 10-fold higher if irreversible AKI present (vs. no AKI)
  - accurately predicted 30-day mortality, length of hospital stay, and organ failure(21).

Supplementary Table 1. Utility of AKI in Predicting Mortality in Cirrhotic Patients Hospitalized With Infection

<table>
<thead>
<tr>
<th></th>
<th>Death</th>
<th>Survival</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>With AKI</td>
<td>56</td>
<td>110</td>
<td>166</td>
</tr>
<tr>
<td>Without AKI</td>
<td>12</td>
<td>159</td>
<td>171</td>
</tr>
<tr>
<td>Total</td>
<td>68</td>
<td>269</td>
<td>337</td>
</tr>
</tbody>
</table>

NOTE. The sensitivity was 56/68 (0.8235), specificity was 159/269 (0.5911), positive predictive value was 56/166 (0.3373) (type I error rate, α), and negative predictive value was 159/171 (0.9298) (type II error rate, β).
• 562 cirrhotic patients over 6 yrs
  ▫ AKI, stratified into 4 groups

• Incidence/mortality
  ▫ Infection/sepsis (46%; 69%)
  ▫ Hypovolemia (32%; 54%)
  ▫ HRS (13%; 85%)
  ▫ Parenchymal (9%; 27%)

• 90 day mortality → worse for HRS
  ▫ adj-HR 3.48 (1.48-8.17)

HRS independently associated with 90 mortality after adjusting for MELD, Na and HE
A modified acute kidney injury classification for diagnosis and risk stratification of impairment of kidney function in cirrhosis

Claudia Fagundes

Etiology and severity of AKI impact mortality in cirrhotic/ACLF patients

A: Stage 1 AKI, SCr < 1.5 mg/dl (low Urine output only)
B: Stage 1 AKI, SCr > 1.5 mg/dl
C: Stage 2/3 AKI (> 2x baseline)
# Methods of assessing renal function in liver disease

<table>
<thead>
<tr>
<th></th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serum</strong> based methods</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Creatinine</td>
<td>• Universally available</td>
<td>• Affected by age, gender, muscle mass, steroids, medications</td>
</tr>
<tr>
<td></td>
<td>• Inexpensive</td>
<td>• Decreased generation in liver disease</td>
</tr>
<tr>
<td></td>
<td>• MELD/AKI scores, current HRS definitions use this</td>
<td>• Bilirubin effect on assay</td>
</tr>
<tr>
<td></td>
<td>• Not affected by age, gender, muscle mass, sepsis</td>
<td>• Lack of standardization of creatinine assays</td>
</tr>
<tr>
<td></td>
<td>• Simple blood test</td>
<td>• Slow to rise in AKI</td>
</tr>
<tr>
<td></td>
<td>• Appears to detect early kidney dysfunction and AKI earlier than serum creatinine</td>
<td>• Underestimates GFR post transplant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Dilution as with all serum markers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Variable performance of Cystatin C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Variable expense</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Results may not be available on a timely fashion</td>
</tr>
<tr>
<td>Serum Cystatin C</td>
<td>• Not affected by age, gender, muscle mass, sepsis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Simple blood test</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Appears to detect early kidney dysfunction and AKI earlier than serum creatinine</td>
<td></td>
</tr>
<tr>
<td>Urine based methods</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary creatinine clearance</td>
<td>• Inexpensive</td>
<td>• Difficult to get accurate collections</td>
</tr>
<tr>
<td></td>
<td>• Avoids dilution issues of serum markers</td>
<td>• Systematically Overestimates GFR in liver disease by 10-15% especially in pts with chronic kidney disease</td>
</tr>
</tbody>
</table>
It is difficult to demonstrate a reduction in GFR in cirrhosis with creatinine alone!

Fig. 1. Relationship between glomerular filtration rate (inulin clearance) and serum creatinine in patients with cirrhosis and ascites.
ARE THERE BETTER MARKERS THAN Creatinine and Urine output?

- Assessment of AKI?
- Differentiate etiology of AKI
  - Prerenal azotemia, hepatorenal syndrome, ATN
  - Cirrhotics/Acute on Chronic Liver Failure (ACLF)
    - Determinants of mortality in absence of transplant
- Post-transplant
  - Predictors of renal recovery/reversibility of AKI
  - Predictors of mortal post transplant
Urinary neutrophil gelatinase-associated lipocalin as biomarker in the differential diagnosis of impairment of kidney function in cirrhosis

PRA n=16
CKD n=14
HRS n=33
ATN n=21

Urinary NGAL
HRS vs. PRA p=0.029
ATN vs. all others, p <0.01

Fig. 1. Box-plot of (A) urine and (B) plasma neutrophil gelatinase-associated lipocalin (NGAL) levels according to the four different causes of impairment of kidney function. The boxes represent the 25th percentile (bottom line), median (middle line), and 75th percentile (top line) values, whereas the whiskers are the lowest datum still within 1.5 IQR of the lower quartile, and the highest datum still within 1.5 IQR of the upper quartile. The Kruskal–Wallis test for each marker was: urine NGAL (p <0.0001) and plasma NGAL (p = 0.31). \(^a_p = 0.029\) vs. pre-renal azotemia. \(^b_p <0.01\) vs. all other groups.

Kidney Biomarkers and Differential Diagnosis of Patients With Cirrhosis and Acute Kidney Injury

Justin M. Belcher,1,2,3 Arun J. Sanyal,4 Aldo J. Peixoto,2,5 Mark A. Perazella,2,5 Joseph Lim,6 Heather Thiessen-Philbrook,7 Naheed Ansari,8 Steven G. Coca,1,2,3 Guadalupe Garcia-Tsao,5,6 and Chirag R. Parikh,1,2,3 for the TRIBE-AKI Consortium

Urinary biomarkers (renal tubular injury):
- NGAL
- IL-18
- Kidney-injury molecule-1 (KIM-1)
- L-FABP
Kidney Biomarkers and Differential Diagnosis of Patients With Cirrhosis and Acute Kidney Injury

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Table 4. Association Between Biomarker Panel and the Diagnosis of ATN

<table>
<thead>
<tr>
<th>Relative Risk*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Markers Positive</td>
</tr>
<tr>
<td>1 Marker Positive</td>
</tr>
<tr>
<td>2 Markers Positive</td>
</tr>
<tr>
<td>3 Markers Positive</td>
</tr>
<tr>
<td>4 Markers Positive</td>
</tr>
</tbody>
</table>

Biomarker cutoffs: NGAL, 365 ng/mL; IL-18, 85 pg/mL; L-FABP, 25 ng/mL; Albumin 44 mg/dL.

*Unadjusted.

Abbreviations: ATN, acute tubular necrosis.
Impact of the Etiology of Acute Kidney Injury on Outcomes Following Liver Transplantation: Acute Tubular Necrosis Versus Hepatorenal Syndrome

More likely to have CKD post LT if ATN present pre-LT

NADIM ET AL.  LIVER TRANSPLANTATION, May 2012
ATN (Non-HRS AKI) impacts post-LT mortality
Plasma Protein Biomarkers Enhance the Clinical Prediction of Kidney Injury Recovery in Patients Undergoing Liver Transplantation

Josh Levitsky, Talia B. Baker, Chunfa Jie, Shubhada Ahya, Murray Levin, John Friedewald, Patrice Al-Saden, Daniel R. Salomon, and Michael M. Abecassis

Table 3. Statistically Significant Plasma Protein Differences Between nAKI, iAKI, and rAKI Validation Groups

<table>
<thead>
<tr>
<th>Group and Protein Comparison</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>nAKI vs. iAKI</td>
<td></td>
</tr>
<tr>
<td>Cystatin C</td>
<td>0.004</td>
</tr>
<tr>
<td>NGAL</td>
<td>0.0363</td>
</tr>
<tr>
<td>TFF-3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>VEGF</td>
<td>0.008</td>
</tr>
<tr>
<td>nAKI vs. rAKI</td>
<td></td>
</tr>
<tr>
<td>Cystatin C</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>KIM-1</td>
<td>0.0024</td>
</tr>
<tr>
<td>NGAL</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>OPN</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TIMP-1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TFF-3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>VEGF</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>iAKI vs. rAKI</td>
<td></td>
</tr>
<tr>
<td>OPN</td>
<td>0.0091</td>
</tr>
<tr>
<td>TIMP-1</td>
<td>0.0194</td>
</tr>
</tbody>
</table>

Table 4. Logistic Regression Models Predicting Reversible AKI: Clinical and Protein Variables and Their Coefficients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Clinical-Covariate-Only Model</th>
<th>Protein-Only Model</th>
<th>Combined-Data Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age status (age &gt; 57)</td>
<td>-2.77</td>
<td></td>
<td>-4.65</td>
</tr>
<tr>
<td>Diabetes (yes)</td>
<td>-2.46</td>
<td></td>
<td>-2.28</td>
</tr>
<tr>
<td>OPN</td>
<td>2.47</td>
<td></td>
<td>1.17</td>
</tr>
<tr>
<td>TIMP-1</td>
<td>0.80</td>
<td></td>
<td>3.54</td>
</tr>
</tbody>
</table>

OPN ~ osteopontin
TIMP-1 ~ tissue inhibitor of metaloproteinase-1

nAKI ~ no AKI
rAKI ~ reversible AKI post-LT
iAKI ~ irreversible AKI post-LT
Therapies for HRS-AKI

(AVP-R1)

Splanchnic vasoconstrictor → Splanchnic and systemic vasoconstriction →

Increased effective arterial blood volume →
Increased arterial pressure →
Increased renal perfusion pressure →

Decreased renal vasoconstrictor systems →

Decreased renal vasoconstriction →

Increased GFR
A Randomized, Prospective, Double-Blind, Placebo-Controlled Trial of Terlipressin for Type 1 Hepatorenal Syndrome

N=56  Albumin 1 g/kg then 20-40 g/day
N=56  Terlipressin 1 mg IV q6h + Albumin

Treatment was continued to day 14 unless
- Success: ↓SCr level to ≤1.5 mg/dL for ≥ 48 hours by day 14
- Failure: Death, dialysis, or transplantation

HRS Reversal 34% vs 13% (p=0.008)

No mortality benefit
Terlipressin 1-2 mg IV q4h

Albumin daily 1g/kg

N=23 Terlipressin/Albumin,
N=23 Albumin alone

Improved renal function
43 vs 8%, p<0.05

No difference in 2 month survival
Terlipressin versus Norepinephrine in the Treatment of Hepatorenal Syndrome: A Systematic Review and Meta-Analysis

Antonio Paulo Nassar Junior\textsuperscript{1*}, Alberto Queiroz Farias\textsuperscript{2}, Luiz Augusto Carneiro d' Albuquerque\textsuperscript{3}, Flair José Carrilho\textsuperscript{2}, Luiz Marcelo Sá Malbouisson\textsuperscript{1}

REVERSAL OF HRS: Norepinephrine vs. Terlipressin

### REVERSAL OF HRS: Norepinephrine vs. Terlipressin

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>Treatment</th>
<th>Control</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alessandria et al. 2007</td>
<td></td>
<td>0.84 (0.52, 1.36)</td>
<td>7/10</td>
<td>10/12</td>
<td>24.91</td>
</tr>
<tr>
<td>Sharma et al. 2008</td>
<td></td>
<td>1.00 (0.54, 1.86)</td>
<td>10/20</td>
<td>10/20</td>
<td>14.83</td>
</tr>
<tr>
<td>Singh et al. 2012</td>
<td></td>
<td>1.11 (0.56, 2.22)</td>
<td>10/23</td>
<td>9/23</td>
<td>11.94</td>
</tr>
<tr>
<td>Ghosh et al. 2013</td>
<td></td>
<td>1.00 (0.71, 1.41)</td>
<td>17/23</td>
<td>17/23</td>
<td>48.32</td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p = 0.904)</td>
<td></td>
<td>0.97 (0.76, 1.23)</td>
<td>44/76</td>
<td>46/78</td>
<td>100.00</td>
</tr>
</tbody>
</table>

**NE vs. Terlipressin in HRS:** No difference in mortality or rates of HRS reversal
AKI in Cirrhosis: Conclusions

• HRS-AKI impacts mortality significantly in the absence of liver transplant (LT).
• Vasoconstrictor therapies (terlipressin, norepinephrine) are associated with reversal of HRS but do not impact mortality in the absence of LT.
• Other causes of AKI in cirrhosis have a significant impact on mortality.
  • The presence of Non-HRS AKI is associated with increased rates of CKD and decreased survival rates post-LT.
• Serum creatinine is confounded by a variety of factors in cirrhotic patients.
• Novel urinary and plasma biomarkers potentially may in the future assist in differentiating
  • Etiology of AKI in cirrhotic patients (Urinary NGAL, IL-18, KIM-1)
  • Reversibility of AKI post-LT (osteopontin, TIMP-1)