Acute Kidney Injury in Cirrhosis

Javier A. Neyra, MD, MSCS, FASN
Assistant Professor
Director, Acute Care Nephrology & CRRT Program

2017 Bruce Lucas Liver Transplant and Hepatology Symposium
Disclosure

• None
Learning Objectives

• Describe potential etiologies of AKI in patients with cirrhosis
• Identify limitations of hepatorenal syndrome diagnosis
• Explain the general management of AKI in patients with cirrhosis
Outline

• AKI and liver cirrhosis: conceptual approach
• Hepatorenal syndrome: more than an exclusion diagnosis
• AKI and liver cirrhosis: treatment strategies
AKI in the Hospital

- AKI occurs in 20% of hospitalized pts (doubles in ICU pts)
- Severely ill patients with AKI have mortality rates up to 50%
- 5-10% hospitalized patients have AKI-D
- One third of AKI survivors will develop CKD within 2 to 5 years
- AKI survivors have higher risk for CVD and HTN

Neyra JA at https://www.kidney.org/atoz/content/AcuteKidneyInjury
Natural history of liver cirrhotic patients

- Development of cirrhosis
- Development of complications

Compensated Cirrhosis → Decompensated Cirrhosis

OLT → Death

AKI

Adapted from D’Amico et al. Hepatology 2006
Two-year survival in liver cirrhotic patients

Adapted from D’Amico et al. Hepatology 2006
AKI in cirrhosis is complex and heterogeneous

INTRINSIC RENAL DISEASE
- ATN
- AIN (drugs)
- GN (IgAN, MPGN)
- Sepsis
- Vasculitis

HEPATORENAL SYNDROME
- Obstructive uropathy
- HRS – AKI
- HRS – CKD

Bile cast: cause or consequence?
Algorithm for AKI inside the box

Clinical Evaluation

Renal U/S (obstruction)

FeNa, FeUrea, urine osm, proteinuria, urine microscopy

FeNa >1-2%
FeUrea 50-65%
RTEC/granular casts
Isosthenuria
Tubular proteinuria ~1g

FeNa <1%
FeUrea <35%
Bland urine
BUN/SCr >20
High Uosm

RBC casts
Dysmorphic RBCs

WBC casts

ATN

Pre-renal

*volume depletion, ADHF, HRS, meds

RPGN/vasculitis

*IgAN, LN, HIVAN, PIGN
*ANCA, anti-GBM dx

AIN

Pyelonephritis

Keys: anamnesis, volume status, hemodynamics, skin lesions, biochemical parameters

if history of obstructive uropathy, malignancy
*Doppler if suspicion of renal infarct, RAS, RVT

*Doppler if suspicion of renal infarct, RAS, RVT
AKI Biomarkers

Bonventre JV et al. Nature 2010
Risk factors:
- Older age
- Diabetes
- CHF
- CKD
- Cirrhosis
- Prior AKI

Insult:
Severe sepsis

Insult:
 Decompensated liver cirrhosis

Markers: SCr and UOP
Cirrhotic pts:
- eGFR overestimates mGFR
- poor functional reserve
- recurrent AKI phenotype is common

Adapted from Chawla and Ronco, KI 2016
Is serum creatinine not enough?

• SCr delays AKI detection as it identifies functional changes in renal clearance but not renal injury
• SCr mandates time-dependent cumulative increment of Cr
• Renal injury or tubular damage can occur with minimal functional loss → subclinical AKI
• Caveats of SCr in cirrhotic pts (overestimation of kidney function): sarcopenia, low protein intake, low urea production, high serum bilirubin may falsely lower SCr, fluid overload

Kathleen D. Liu, MD; B. Taylor Thompson, MD; Marek Ancukiewicz; Jay S. Steingrub, MD; Ivor S. Douglas, MD; Michael A. Matthay, MD; Patrick Wright, MD; Michael W. Peterson, MD; Peter Rock, MD; Robert C. Hyzy, MD; Antonio Anzueto, MD; Jonathon D. Truwit, MD, MBA; for the National Institutes of Health National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Network

Table 1. Development of AKI by treatment group before and after adjustment of serum creatinine for fluid balance

<table>
<thead>
<tr>
<th>Renal Outcomes</th>
<th>Liberal</th>
<th>Conservative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not</td>
<td>Adjusted</td>
</tr>
<tr>
<td>AKIN stage 1, no. (%)</td>
<td>253 (51%)</td>
<td>328 (66%)</td>
</tr>
<tr>
<td>AKIN stage 2, no. (%)</td>
<td>54 (11%)</td>
<td>106 (21%)</td>
</tr>
<tr>
<td>AKIN stage 3, no. (%)</td>
<td>75 (15%)</td>
<td>89 (18%)</td>
</tr>
</tbody>
</table>

AKI, acute kidney injury; AKIN, Acute Kidney Injury Network.

*There was no difference in the incidence of AKI by pulmonary artery catheter vs. central venous catheter management groups.

1000 critically-ill pts from FACT trial

Cumulative Fluid Balance and Mortality in Septic Patients With or Without Acute Kidney Injury and Chronic Kidney Disease

Javier A. Neyra, MD, MSCS; Xilong Li, PhD, MS; Fabrizio Canepa-Escaro, MD; Beverley Adams-Huet, MS; Robert D. Toto, MD; Jerry Yee, MD; S. Susan Hedayati, MD, MHS for the Acute Kidney Injury in Critical Illness Study Group
<table>
<thead>
<tr>
<th>ETOH Cirrhosis Ascites</th>
<th>Preceding Event</th>
<th>Serum Sodium (mEq/L)</th>
<th>SBP (mmHg)</th>
<th>Bilirubin (mg/dL)</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>GI bleeding</td>
<td>129</td>
<td>100</td>
<td>2 - 16</td>
<td>“some hyaline &amp; granular casts, albumin, RBCs”</td>
</tr>
<tr>
<td>(n = 8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group II</td>
<td>Paracentesis</td>
<td>121</td>
<td>100</td>
<td>2.6 - 17</td>
<td>“trace albumin, occasional RBCs”</td>
</tr>
<tr>
<td>(n = 3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group III</td>
<td>Progressive jaundice</td>
<td>124</td>
<td>90</td>
<td>4 - 34</td>
<td>“albumin, RBCs”</td>
</tr>
<tr>
<td>(n = 5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group IV</td>
<td>None</td>
<td>135</td>
<td>90</td>
<td>1.6 - 15</td>
<td>“bland”</td>
</tr>
<tr>
<td>(n = 5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- All pts died with kidney failure and hepatic coma
- **Kidney pathology post-mortem** of 18/22 patients revealed occasional minimal tubular cell flattening and bile staining, but were essentially normal
HRS: A Functional Disorder in Renal Circulation


Ring-Larsen H. Denmark. Scan J Clin Lab Invest 1977

Creatinine Clearance

*ml/g-min*
• 7 kidneys from pts with liver cirrhosis and HRS were transplanted into 7 ESRD recipients
• Good allograft function by day 14: 6/7 (86%)
• 4 kidneys achieved stable kidney function for >6 months
RECOVERY FROM “HEPATORENAL SYNDROME” AFTER ORTHOTOPIC LIVER TRANSPLANTATION

Shunzaburo Iwatsuki, M.D., Mordecai M. Popovtzer, M.D., Jacques L. Corman, M.D., Makoto Ishikawa, M.D., Charles W. Putnam, M.D., Fred H. Katz, M.D., and Thomas E. Starzl, M.D., Ph.D.

- 3 pts with ESLD and HRS underwent OLT
- All 3 gained adequate kidney function within 2 weeks of OLT
HRS: Pathophysiology

1. H2O and sodium retention
2. Ascites
3. Hyponatremia
4. ↓ GFR

↑ Effective Circulating Volume

↓ Effective Circulating Volume

↑ RAAS

↑ SNS

↑ renal vasoconstriction

↑ NO

portal hypertension

↓ NO

vasopressin release

splanchnic/systemic vasodilation

cirrhotic cardiomyopathy

tachycardia ↑ CO

baroreceptor activation

Adapted from Ayach T. IMGR 2017
HRS: Precipitating Factors

Adapted from Ayach T. IMGR 2017
HRS: Incidence

*Suneja M et al., Int J Nephrol 2016*

*Pant C et al., J Investig Med 2016*
# HRS: Definitions

<table>
<thead>
<tr>
<th>Main Clinical Characteristics of Type 1 and Type 2 Hepatorenal Syndrome (HRS)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type 1 HRS</strong></td>
</tr>
<tr>
<td>• Acute and rapid deterioration in renal function (serum creatinine ≥ 2.5 mg/dl or 220 μmol/l in less than 2 weeks)</td>
</tr>
<tr>
<td>• Occurs in parallel with the failure of other organs or systems (e.g., coagulopathy, hepatic encephalopathy)</td>
</tr>
<tr>
<td>• In cirrhosis, is a form of acute-on-chronic liver failure</td>
</tr>
<tr>
<td>• Frequently follows a precipitating event, mainly bacterial infection</td>
</tr>
<tr>
<td>• Rapidly fatal without treatment: mean survival 2 to 3 weeks</td>
</tr>
<tr>
<td><strong>Type 2 HRS</strong></td>
</tr>
<tr>
<td>• Moderate stable renal impairment (average serum creatinine 2 mg/dl [176 μmol/l])</td>
</tr>
<tr>
<td>• Mainly causes refractory ascites</td>
</tr>
<tr>
<td>• Mean survival without treatment: 6 months</td>
</tr>
</tbody>
</table>
**Diagnostic Criteria HRS-1**

**Caveats:**
- How to assess partial response to volume expansion (SCr improvement, hemodynamic parameters, etc.)?
- Limited urine microscopy cutoffs without clinical context (granular casts, RTEs, etc.)?
- Abdominal perfusion pressure parameters (IAH, ACS)?
- Urine electrolytes?

---

**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

*Gut 2015.
Is paracentesis a precipitating factor?
Role of abdominal compartment syndrome

Cirrhotics with AKI (n = 19)

| IAP (mmHg) | 22 (18 – 24) |

\[ \text{APP} = \text{MAP} - \text{IAP} \]
International Club of Ascites (ICA-AKI) new definitions for the diagnosis and management of AKI in patients with cirrhosis

Gut 2015

<table>
<thead>
<tr>
<th>Subject</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline sCr</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 if occurred within the
  
**Staging of AKI**

- **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**

<table>
<thead>
<tr>
<th>No response</th>
<th>Partial response</th>
<th>Full response</th>
</tr>
</thead>
<tbody>
<tr>
<td>No regression of AKI</td>
<td>Regression of AKI stage with a reduction of sCr to ≥0.3 mg/dl (26.5 μmol/L) above the baseline value</td>
<td>Return of sCr to a value within 0.3 mg/dl (26.5 μmol/L) of the baseline value</td>
</tr>
</tbody>
</table>
### KDIGO: AKI Definition

**Table 2 | Staging of AKI**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Serum creatinine</th>
<th>Urine output</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5–1.9 times baseline OR ≥ 0.3 mg/dl (≥ 26.5 µmol/l) increase</td>
<td>&lt; 0.5 ml/kg/h for 6–12 hours</td>
</tr>
<tr>
<td>2</td>
<td>2.0–2.9 times baseline</td>
<td>&lt; 0.5 ml/kg/h for ≥ 12 hours</td>
</tr>
<tr>
<td>3</td>
<td>3.0 times baseline OR Increase in serum creatinine to ≥ 4.0 mg/dl (≥ 353.6 µmol/l) OR Initiation of renal replacement therapy OR, in patients &lt; 18 years, decrease in eGFR to &lt; 35 ml/min per 1.73 m²</td>
<td>&lt; 0.3 ml/kg/h for ≥ 24 hours OR Anuria for ≥ 12 hours</td>
</tr>
</tbody>
</table>

KDIGO Guidelines 2012
**HRS-1: FENa < 1% is always present but not diagnostic**

FENa according to biopsy-proven diagnoses

- **FENa <1% to diagnose HRS**

Alsaad & Wadei, World J Hepatol 2016
HRS-1: Use of novel urinary biomarkers

Belcher et al TRIBE Hepatology 2014
Summary: HRS diagnosis

- HRS is much more than an exclusion diagnosis
- HRS diagnosis is complex and requires comprehensive clinical evaluation (biochemical, hemodynamic, urine microscopic) and sometimes therapeutic trials (albumin, LVP, vasopressors)
- HRS-1 and ATN may coexist
- HRS definition has caveats that should be surpassed in clinical practice
- HRS + recurrent AKI or CKD phenotypes are not fully recognized
- Biomarkers of early renal dysfunction or injury are needed
Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers

<table>
<thead>
<tr>
<th>Surgery</th>
<th>48h</th>
<th>72h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoidance of nephrotoxic agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Withholding of ACEi and ARBs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Close monitoring of SCr and urine output</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avoidance of Hyperglycaemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consider alternatives to radio-contrast agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optimization of volume status and haemodynamic parameters</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Graph showing the prevention of AKI](image)

Meersch et al. Intensive Care Med 2017
HRS: Treatment

Cirrhosis

TIPS

Portal hypertension

Splanchnic/systemic vasodilatation

↓ Effective arterial blood volume

Activation of neurohormonal systems:

Renin-angiotensin

Renal vasoconstriction

Decreased GFR

Hepatorenal syndrome

Vasoconstrictors + Albumin

Liver transplant

Adapted from Ayach T. IMGR 2017
HRS: Treatment

3-month survival

n = 99

Transplanted: 97% (34/35)
Responders: 41% (7/17)
Non-responders: 4% (2/47)

Transplant-free

HRS: Treatment

- Vasoconstrictors
  - Dopamine
  - Midodrine / Octreotide
  - Terlipressin
  - Ornipressin
  - Vasopressin
  - Norepinephrine
HRS: Treatment
Midodrine + Octreotide vs. Dopamine
Prospective Non-Parallel Trial

% improved Cr by day 5

- Midodrine/Octreotide: 60%
- Dopamine: 0%

Angeli et al. Hepatology 1999

MAP Change

Angeli et al. Hepatology 1999
HRS: Terlipressin (U.S. RCTs)

Sanyal et al. Gastroenterol 2008
RCT: terlipressin vs placebo, n=112

- Terlipressin: 34%
- Placebo: 12.5%
- HR = HRS reversal
- TS = treatment success

p = 0.008

Boyer et al. Gastroenterol 2016
RCT: terlipressin vs placebo, n=196 (REVERSE)

- Responded to Terlipressin: 13.7%
- Did not respond to Terlipressin: 3.2%

p < 0.01

MAP rise (mmHg)
HRS: Terlipressin vs Norepinephrine

Alessandria et al. Hepatology 2007

- Norepinephrine (n=10): 70%
- Terlipressin (n=10): 83%

Singh et al. J Hepatol 2012

- Norepinephrine (n=23): 43%
- Terlipressin (n=23): 39%
HRS: Raising MAP

Terlipressin

Placebo

Boyer et al. J Hepatol 2011
HRS: Therapeutic response to vasoconstrictors in HRS parallels increase in MAP

Pooled analysis of 21 studies
10 dual-arm
11 single-arm
(37 cohorts)

Velez JC et al. AJKD 2011
True HRS subjects (n = 27): Change in SCr from Baseline, Stratified by Quartile of Peak Change in MAP

- Quartile 1 (-9.0 to +0.0 mmHg)
- Quartile 2 (+0.8 to +4.9 mmHg)
- Quartile 3 (+5.3 to +15.6 mmHg)
- Quartile 4 (+15.9 to +20.9 mmHg)

P-trend = 0.002

Velez JC et al. Nephron 2015
HRS: Raising MAP

- Renal blood flow autoregulation curve is shifted to the right in pts with liver cirrhosis (effect of SNS activation)


$\sim 65$ mmHg

$\sim 91$ mmHg
Summary: HRS treatment

• Albumin + vasoconstrictor therapy for at least 48-72 hours may improve kidney function in ~40-60% of HRS pts

• Reversal of HRS with vasoconstrictor therapy without a significant increase in MAP is unlikely to occur

• In the U.S. norepinephrine seems to be a valid alternative to midodrine/octreotide, particularly when the MAP target is not achieved

• Increase in MAP ~10-15 mmHg (and optimizing APP) is a reasonable treatment strategy in HRS-1 but RCTs are needed to examine safety and efficacy