Kidney Diseases in Liver Cirrhosis

Prof. Marek Hartleb

Department of Gastroenterology and Hepatology
Medical University of Silesia
Katowice, Poland
Pathomechanism of AKI in cirrhosis

Effective hypovolemia

Noradrenaline
Angiotensin
Vasopressin

Vasoconstriction

Hypoperfusion
Hypercreatinemia (AKI)
Sodium and water retention

Vasodilatation

Duodenum
Jejunum
Ileum empties into cecum (large intestine)
Physiological factors regulating renal perfusion/function

Cardiac output (CO)

Mean arterial pressure (MAP)

Intraabdominal pressure (IAP)

Portal cardiomyopathy

Splanchnic arterial vasodilatation

Abdominal Compartment Syndrome (ascites)

Arterial tone a. afferens

Angiotensin II
Norepinephrine
Vasopressin

Vascular autoregulation

Reduced synthesis of kallikrein and PG-E₂
Increased synthesis of ET-1
### Definition of Acute Kidney Injury (AKI) according to AKI Network (AKIN)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Increase of creatinine level / 48 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>↑ 0.3 mg/dl OR ↑ 1.5-2 x baseline</td>
</tr>
<tr>
<td>2</td>
<td>≥ 2-3 x baseline</td>
</tr>
<tr>
<td>3</td>
<td>↑ 0.3 mg/dl if baseline ≥ 4 mg/dl OR</td>
</tr>
<tr>
<td></td>
<td>&gt; 3 x baseline OR If renal replacement therapy was started</td>
</tr>
</tbody>
</table>

- Known or presumed to have occurred within the prior 3 months
- Single value of sCr is not sufficient to diagnose AKI

Modified by IAC
Extra-renal influences on creatinine levels in cirrhosis

- Protein intake
- Muscle mass
- Sepsis

Production

- Creatine conversion to creatinine
- Volume of distribution

Measurement

- Hyperbilirubinemia
- Tubular secretion

Excretion

- Drugs: Trimethoprim, Cimetidine
Relationship between serum creatinine level ($S_{cr}$) and GFR

- Creatinine overestimates GFR in cirrhosis

Creatinine ≥ 1.5 mg/dl in cirrhosis

11% GI bleeding
34% Spontaneous bacterial peritonitis
17% Other bacterial infection
40-49% Critically ill patients hospitalized in ICU

24% in outpatients with cirrhosis within one-year of the first episode of ascites

26-47% in-patients (mostly AKIN stage 1)

Cardenas A et al. Hepatology 2001; 34: 671
Carvalho GC et al. Ann Hepatol 2012; 11:90
Fagundes et al. J Hepatol 2013; 59: 474
Piano S et al. J Hepatol 2013; 59: 482
Hepatorenal diseases

Obstructive nephropathy

< 1%

Hypoperfusion ~ 70%

⅔

organic

¼

functional

Pre-renal failure

AKI

AKI

ACLF

Chronic kidney disease

Glomerulo-nephritis (HCV)
Diabetic nephropathy (NASH)
IgA-nephropathy (ALD)

Cirrhosis & SIR (ACLF)

HRS: Hepatorenal syndrome; ATN: acute tubular necrosis, ACLF: acute-on-chronic liver failure

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Cirrhosis

Portal (sinusoidal) hypertension

Mesenteric/systemic vasodilatation

Effective hypovolemia

Activation of neurohormonal systems

Renal sodium / water retention

Ascites & Hyponatremia

Renal vasoconstriction

Renal blood perfusion

HRS

Bacterial infection

Vasodilators (drugs)

Aggressive paracentesis
Typical scenario:
Diuretic-resistant ascites $\rightarrow$ SBP $\rightarrow$ HRS-1

Antibiotic & albumin
day 1 and 3
Cirrhosis

Portal (sinusoidal) hypertension

Mesenteric/systemic vasodilation

Effective volemia ↓

Activation of neurohormonal systems

Renal sodium / water retention

Ascites & Hyponatremia

Renal vasoconstriction

Renal blood perfusion

Ascites & Hyponatremia

Bacterial infection
Vasodilators (drugs)
Aggressive paracentesis

Overdiuresis (drugs)
Vomiting
GI bleeding
Diarrhea (infective, drugs)

NSAIDs

CO ↓

HRS

Sepsis
Propranolol
Hepatorenal syndrome

Diagnostic criteria

- Diagnosis of AKI according to IAC-AKIN criteria
- Cirrhosis & ascites
- No improvement (sCr < 1.5 mg/dl) after at least 2 days of diuretic withdrawal and plasma volume expansion with albumin 1g/kg/24 h (max. 100 g)
- Absence of shock (septic or hemorrhagic)
- Absence of parenchymal kidney disease (urine protein < 500 mg/24 h and/or erythrocytes < 50 hpf)
- No current or recent use of nephrotoxic agents

Urine volume < 400 ml/24 h is not obligatory
Hepatorenal syndrome (HRS)

In HRS the pathology exclusively regards the renal vascular system.

End-stage cirrhosis

Post-mortem

Structural changes in 77% of biopsies (mostly tubular degenerative lesions)

Russ KB et al. J Clin Transl Hepatol 2015, 3, 195
Acute kidney injury

- Unrecognized AKI
- Septic shock
- Hemorrhagic shock
- Nephrotoxic drugs (NSAIDs, aminoglycosides)
- Radiological contrasts

- Diuretics
- Diarrhea
- SBP (other infection)
- Paracentesis

Prerenal azotemia → HRS-1 → Acute tubular necrosis

Degree of renal hypoperfusion

- $U_{Osm} > 500$ mOsm/kg
- $FENa < 1\%$
  - Urine exam: No casts
  - Volume expansion $\rightarrow$ sCr normalization

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- $FENa < 1\%$
  - Urine exam: No casts
  - Volume expansion $\rightarrow$ No sCr normalization

- $U_{Osm} < 350$ mOsm/kg
- $FENa > 2\%$
  - Urine exam: Casts granular/epithelial
  - Renal biopsy ?
Biomarkers of tubular necrosis

- nearly 30 primarily tubular markers
- differentiate well pre-renal azotemia from ATN
- more than one marker should be used

Belcher JM et al. Hepatology 2014; 60: 622
Hepatorenal diseases

Obstructive nephropathy < 1%

Pre-renal failure

Hypoperfusion ~ 70%

⅔

functional

有机

有机

AKI

AKI

AKI

Chronic kidney disease

HRS

1/3

triggered HRS

spontaneous HRS

Cirrhosis & SIR (ACLF)

HRS: Hepatorenal syndrome; ATN: acute tubular necrosis, ACLF: acute-on-chronic liver failure

AKI in acute-on-chronic liver failure (ACLF)

Multiorgan failure
- **Kidney**
- Cerebral
- Circulatory
- Respiratory
- Coagulation

**Liver cirrhosis +**
- alcoholic hepatitis
- sepsis
- reactivation of HBV infection
- acute hepatitis A or E
- PVT
- ischemia
- drug-induced liver injury

Degree of SIR correlates with number of organ failures

- Another mechanism of AKI *(≠hypoperfusion)*
- Another treatment *(albumin, PTX, N-acetylcysteine??)*

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**IL-1,6,8 TNFα**

**SIR & oxidative stress**

**Table: Scoring system for ACLF**

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Score = 1</th>
<th>Score = 2</th>
<th>Score = 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver, bilirubin (mg/dl)</td>
<td>&lt;6</td>
<td>6≤12</td>
<td>&gt;12</td>
</tr>
<tr>
<td>Kidney, creatinine (mg/dl)</td>
<td>&lt;2</td>
<td>2&lt;3.5</td>
<td>≥3.5 or renal replacement</td>
</tr>
<tr>
<td>Brain, grade (West-Haven)</td>
<td>0</td>
<td>1-2</td>
<td>3-4</td>
</tr>
<tr>
<td>Coagulation, INR</td>
<td>&lt;2.0</td>
<td>2.0≤2.5</td>
<td>≥2.5</td>
</tr>
<tr>
<td>Circulation, MAP (mmHg)</td>
<td>≥70</td>
<td>&lt;70</td>
<td>Vasopressors</td>
</tr>
<tr>
<td>Respiratory PaO₂/FiO₂</td>
<td>&gt;300</td>
<td>300≤ and &gt;200</td>
<td>&lt;200</td>
</tr>
<tr>
<td>or SpO₂/FiO₂</td>
<td>&gt;357</td>
<td>214 and ≤357</td>
<td>≤214</td>
</tr>
</tbody>
</table>

*Arroyo V. et al. J Hepatol 2015; 62: 131*
AKI in cirrhosis - prognosis

In patients with sCr > 1.5 mg/dl
- higher probability of being transferred to intensive care unit
- longer hospitalization
- higher short-term mortality

\[
\text{MELD Score} = 10 \times \left[ (0.957 \times \ln sCr) + (0.378 \times \ln \text{Bilirubin}) + 1.12 \times \ln \text{INR} \right] + 6.43
\]

Survival is influenced not only by the stage of renal dysfunction but also by the progression on follow-up

Belcher JM et al. Hepatology 2013; 57:753
Wong F et al. J Hepatol 2015; 62: 739
Survival of patients with liver cirrhosis without HRS, with HRS-2 and HRS-1

Median survival
HRS-1 = ~ 2 weeks
HRS-2 = ~ 5 months

sCr ≥ 2.5 mg/dl during 2 weeks

**General management principles in case of increase of creatinine level**

- **Withdrawal of diuretics**
  
  Withdrawal of potentially nephrotoxic drugs, vasodilators or NSAIDs (review drug chart including OTC drugs)

- **Plasma volume expansion**
  
  Albumin iv 1 g/kg/24 hr (max. 100 g)* or blood in case of GI bleeding (re-evaluation after 2 days)

- **Antibiotic** (bacterial infection?)

- **Urine analysis** (leukocytes?, casts?, erythrocytes?)

- **Ultrasound of kidneys**

* monitored by central venous pressure
Treatment of AKI in cirrhosis (pre-renal, HRS, ATN)

Effective hypovolemia

Norpinephrine
Angiotensin
Vasopressin

Vasoconstriction

Volume expander (albumin)

Splanchnic vasoconstrictor (terlipressin, norepinephrine, octreotide)

Vasodilatation
HRS Treatment
terlipressin & albumin

Efficacy of terlipressin in HRS-1:
HRS reversal, survival

Single predictor of HRS-1 reversal:
was baseline serum creatinine, importance of MAP

Sanyal AJ et al. Gastroenterology 2008; 134: 1360

Boyer TD et al. J Hepatol 2011; 55: 315
Acute Kidney Injury

Treatment

Pre-renal azotemia → HRS-1 → Acute tubular necrosis

Degree of renal hypoperfusion

- Vascular system repletion (albumin, crystalloids)
- Vasoconstrictor & albumin
- Renal replacement therapy

No response ~ 50%
1. Normal perfusion (e.g. ACLF)
2. Chronic renal disease
3. Severe injury (ATN)
Which vasoconstrictor is the best?

Meta-analysis: 4 studies; 154 patients with HRS

**Norepinephrine**
(n=76)

**RESULTS**
Reversal of HRS: 44/76 (74%)
30-day mortality: 36/76 (47%)
Side effects: 6/76 (7.9%)

Norepinephrine requires continuous i.v. infusion.

Cavallin M et al. Hepatology, 2015, 62, 567

RCT: 49 patients with HRS

**MID + OCT + ALB**
(n=22)

**TER + ALB**
(n=27)

**RESULTS**
Reversal of HRS:
6/21 (28.6%)
19/27 (70.4%) p=0.01


Cavallin M et al. Hepatology, 2015, 62, 567
HRS Treatment
terlipressin & albumin

Meta-analysis:
8 RCTs; 378 pts HRS-1

All causes mortality (3 months)
↓ 15%

Mortality due to HRS alone (3 months)
↓ 9%

Response to treatment: 40-60% (mean recovery time 7 days)
Early relapse after response: 5-10%

Hiremath SB et al. Indian J Pharmacol 2013; 45:54
Gluud LL et al. Hepatology 2010; 51: 576
Treatment
role of albumin

Non-randomized study

TER & ALB vs TER alone

Reversal of HRS: 77% vs 25%

Ortega R et al. Hepatology 2002; 36: 941

- Meta-analysis of 8 clinical studies comprising 547 patients with HRS-1
- Pooled reversal of HRS was 49.5%
- Neither survival nor reversal of HRS was influenced by vasoconstrictor type/dose or treatment duration

Salerno F et al. BMC Gastroenterology 2015; 15: 167
Hepatorenal syndrome
Management of non-responders to TER & ALB

• Dialysis
  
  **Conclusions:** Justified as bridge to liver transplantation or while awaiting reversal of an acute liver failure or ACLF (e.g., alcoholic hepatitis).

  **Classical indications:** Severe volume overload, metabolic acidosis, hyperkalemia, symptomatic uremia

• Extracorporeal liver assist devices: Helios (FPSA) and MARS

  **Conclusions:** Improve encephalopathy, sCr and bilirubin level but do not improve short-term survival

• TIPS

  **Conclusions:** reduces portal hypertension and ascites, effect on central volemia, improves indirectly renal function but patients with AKI too sick to undergo TIPS (encephalopathy)

Kribben et al. Gastroenterology 2012
Banares et al. Hepatology 2013
Liver transplantation (LT)

HRS-1

99 pts with HRS-1 treated with **TERLIPRESSIN** or **PLACEBO**

35% underwent LT

Boyer TD et al. Liver Transp. 2011; 17: 1328
Patients with liver cirrhosis have natural tendency to develop AKI that is assoc. with poor prognosis

Definition of HRS-1 has changed according to AKIN, but still is based on exclusion criteria and creatinine level that is imperfect indicator of renal function in cirrhosis

HRS is not the unique, and probably also not the commonest form of AKI in patients with cirrhosis

AKI is potentially reversible disease but type of therapy depends on type of renal failure
The standard treatment of HRS is vasoconstrictor combined with albumin (+ withdrawal of diuretics).

The goal of therapy is to reverse in a very short time window the kidney failure before it leads to irreversible structural renal damage and death.

An estimated 40 to 60% of patients respond to the combination therapy with reversal of kidney failure.

HRS-1 signals the need for immediate LT, which is the only definitive treatment.