A hepatologist’s view of AKI in liver disease

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KIDNEYCON 2018
Little Rock – April 7, 2018
Clinical Case 1

- AKI of patient on diuretics and edema
- Nephrology says diuretics
- Worsening of kidney function
- Improvement after diuretics are improved
Issues to Discuss from Case 1

- Pathophysiology of AKI – underfilling theory
- Type of AKI: prerenal / parenchymal / post-renal / HRS
- Diuretics toxicity
- Cardiorenal vs decreased effective intravascular volume
- Differences in diuretic use:
  - With CKD
    - NSAIDs damage (1 dose → AKI / vasodilators damage / radiocontrast)
    - No dialysis to support further kidney damage – certain death
  - With HFrEF
    - IV lasix and doubling of diuretics
    - No mortality associated to extrapulmonary fluid overload
General Concepts

• AKI occurs in 20-50% of inpatients with cirrhosis
• Annual incidence 32-54% in decompensated outpatients
• Associated with increased mortality (>60% at 1 year)

- Per 1 unit increase in Cr
  2.6-fold increase in mortality

• HRS diagnosis is critical
  – 70-80% mortality if nonresponsive or untreated
  – Response increases survival and bridging to transplantation
Portal Hypertension and AKI: Underfilling Theory

- CIRRHOSIS
  - Portal hypertension
  - Splanchnic arterial blood volume
    - Reduced effective arterial blood volume
    - Activated vasoconstrictor systems
      - Vasoconstriction of extrasplanchnic vascular beds
      - Renal vasoconstriction
        - Activation of renal vasodilators
        - Imbalance of vasoactive factors
          - Maintained renal perfusion
            - HEPATORENAL SYNDROME

- Inflammation
- Cardiomyopathy
Pathophysiology of AKI in cirrhosis

- **Precipitants**
  - Infection, LVP, vasodilators
  - Diarrhea, diuretics, GI bleed
  - NSAIDS
  - Sepsis

- **Mechanism**
  - Portal hypertension
    - Splanchnic/systemic vasodilatation
      - Effective blood volume
      - Arterial underfilling
    - SNS, RAAS, ADH
      - Renal vasoconstriction
      - Reduced GFR

- **Clinical correlates**
  - SVR, MAP
  - Cardiac output
  - Ascites, Hyponatremia
  - Worsening liver function
  - Relative decline in cardiac output
  - Progressive hypoperfusion

- **Acute tubular necrosis**
  - Progressive hypoperfusion
  - Hepatorenal syndrome

Why having a new AKI/HRS definition?

• Creatinine is a poor marker of kidney injury

Dynamic Δ in Cr predict better than a fixed value

AKI Etiology in Cirrhosis

Pre-Renal (Hypovolemia)
- Diuretics / Laxatives
- GI bleeding
- Cardiorenal

Post-Renal (Obstructive)
- Nephrolithiasis
- BPH
- Urothelial tumor

Renal (Parenchymal)
- ATN (ischemic, drugs)
- AIN
- GN (cryoglobulinemia)
- HRS
- IgA nephropathy
- Bile cast nephropathy
- Sepsis / Inflammation
- T2DM / Hypertension
- Other (disease specific)

60-70%

<1%

30%

15-20%

Pre-Renal vs. Renal AKI

- Majority of cases are pre-renal
  - Keep in mind limited usefulness of PE and common biomarkers

<table>
<thead>
<tr>
<th>Physical Exam</th>
<th>Common Biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edema, ascites, anasarca</td>
<td>BUN:Cr</td>
</tr>
<tr>
<td>JVD $\Rightarrow$ PoPH in 5%</td>
<td>UNa and FeNa</td>
</tr>
<tr>
<td>Lungs auscultation</td>
<td>Urine osmolality</td>
</tr>
</tbody>
</table>

- Potential role for FEUrea?
  - 100 patients (retrospective adjudication of ATN, HRS, prerenal)

  ATN vs. Non-ATN, AUC: **0.96** (0.91-1.0)  
  - CUV 33 $\Rightarrow$ PPV 96% / NPV 96%

  HRS vs. Non-HRS, AUC: **0.87** (0.78-0.97)  
  - <21 more likely HRS vs. prerenal
Pre-Renal vs. Renal AKI

• Intravascular volume status evaluation
  – CVP previously recommended → TTE now?

CVP-Based: Dose of albumin 40 – 600 g (great variation from patients and days)

Peron. Am J Gastroenterol 2005;100:2702
Pre-Renal vs. Renal AKI

- As a rule, treat as pre-renal:
  
  **Step 1** → STOP ALL DIURETICS / Nephrotoxics

  **Step 2** → Start IV Albumin

- Adhere to recommendations
- Listen to the Lungs!
- Check Albumin
- 1 g/kg for 48 hrs (max 100 g/d)
  Then 25-50 g/d
- Avoid pulmonary edema
- ≤5 mg/dL

Volume overload in 30%

Shasthry. Liver Int 201737:1167
Clinical Case 2

- AKI not responding to albumin
- Lack of response to midodrine and octreotide
- Jumping to NE
Issues to Discuss from Case 2

• HRS classification and historical perspective
• Clinical trials of vasopressors
• Terlipresin studies
Hepatorenal syndrome (HRS)

- Hepatorenal syndrome
  - “VERY OLD” Definition (International Ascites Club 1996)

<table>
<thead>
<tr>
<th>MAJOR Criteria</th>
<th>Minor Criteria</th>
</tr>
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<tbody>
<tr>
<td>Chronic or acute advanced liver failure w/P-HTN</td>
<td>U volume &lt;500 mL/d</td>
</tr>
<tr>
<td>Low GFR: Cr &gt;1.5 mg/dL or CrCl &lt;40 mL/min</td>
<td>U sodium &lt;10 mEq/L</td>
</tr>
<tr>
<td>No shock, infection, nephrotoxins, volume depletion</td>
<td>U osmolality &gt; P</td>
</tr>
<tr>
<td>No improvement after 1.5 L of volume expansion</td>
<td>U red blood cells &lt;50 p/HPF</td>
</tr>
<tr>
<td>Proteinuria &lt;500 mg/d</td>
<td>Serum Na &lt;130 mEq/L</td>
</tr>
<tr>
<td>No US evidence of obstructive uropathy or CKD</td>
<td></td>
</tr>
</tbody>
</table>
HRS Definition: ICA 1996

- Hepatorenal syndrome
  - “VERY OLD” Definition (International Ascites Club 1996)

<table>
<thead>
<tr>
<th>HRS Type I</th>
<th>HRS Type II</th>
</tr>
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<tbody>
<tr>
<td>Doubling of Cr to &gt;2.5</td>
<td>Increase in Cr to &lt;2.5</td>
</tr>
<tr>
<td>Develops in &lt;2 weeks</td>
<td>Develops slowly</td>
</tr>
<tr>
<td>Precipitating factor (i.e. in 30% of SBP)</td>
<td>Dominant feature is refractory ascites</td>
</tr>
</tbody>
</table>
HRS Definition: Survival Implications

*Median survival after onset of renal failure
HRS Definition: ICA 1996

• Flaws in the VERY OLD definition
  – CrCl not accurate enough
    • Cr is secreted by renal tubules in ESLD
    • Difficulties in keeping an accurate 24-h collection
  – ATN frequently presents with oliguria and UNa <10
  – High serum bilirubin favors UNa >10
  – Volume expansion with NaCl not as effective as with albumin
  – Complete resolution of infectious process is not mandatory
    • Would delay initiation of albumin and vasoconstrictors
  – Inaccuracies in urine sediment
    • Biliary staining of sediment can be read as “granular casts”
Creatinine underestimates GFR in cirrhosis

Dietary and de novo creatine sources are decreased

Poor dietary intake
Cirrhosis → Cr synthesis & distribution (ascites)
Sarcopenia 40-60%

Creatinine overestimates GFR in cirrhosis

Durand. Curr Opin Crit Care 2017;23:457
Duarte-Rojo. Liver Transpl 2018;24:122
Why having a new AKI/HRS definition?

Creatine (Cr) and Creatinine (Crn)

Wyss. Physiol Rev 2000;80:1107
Creatinine underestimates GFR in cirrhosis

Chu. Drug Metab Dispos 2016;44:1498
HRS Definition: ICA 2005

• Hepatorenal syndrome
  – “OLD” Definition (International Ascites Club 2005)

<table>
<thead>
<tr>
<th>Diagnosis of Hepatorenal Syndrome – ICA 2005</th>
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<tbody>
<tr>
<td>Cirrhosis with ascites</td>
</tr>
<tr>
<td>Serum creatinine &gt;1.5 mg/dL</td>
</tr>
<tr>
<td>No response after ≥2 days without diuretics and volume expansion with albumin (1 g/kg/d – maximum of 100 g/d)</td>
</tr>
<tr>
<td>Absence of shock</td>
</tr>
<tr>
<td>No current or recent treatment with nephrotoxic agents</td>
</tr>
<tr>
<td>Absence of evident parenchymal kidney damage:</td>
</tr>
<tr>
<td>• Proteinuria (&gt;500 mg/d)</td>
</tr>
<tr>
<td>• Microhematuria (&gt;50 RBC/HPF)</td>
</tr>
<tr>
<td>• Abnormal renal US</td>
</tr>
</tbody>
</table>

Eliminated: CrCl, UNa, UVol & Osmol Absence of infection
HRS Definition: ICA 2005

- Flaws in the definition
  - Target Cr of >1.5 not meet by sarcopenic patients

- Urinary volume removed from definition
HRS Definition (ICA 2015): First Diagnose AKI!

• New criteria for AKI
  – AKI-ICA: acute kidney injury, International Club of Ascites

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<thead>
<tr>
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<th>Definition</th>
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<tbody>
<tr>
<td><strong>AKI</strong></td>
<td>• ↑ sCr ≥0.3 mg/dL in last 48 hours</td>
</tr>
<tr>
<td></td>
<td>• ↑ sCr ≥50% from baseline within last 7 days*</td>
</tr>
<tr>
<td><strong>AKI Staging</strong></td>
<td>Stage 1</td>
</tr>
<tr>
<td></td>
<td>• sCr ≥0.3 mg/dL or</td>
</tr>
<tr>
<td></td>
<td>• x1.5-2 baseline</td>
</tr>
<tr>
<td></td>
<td>Stage 2</td>
</tr>
<tr>
<td></td>
<td>• &gt;x2-3 baseline</td>
</tr>
<tr>
<td></td>
<td>Stage 3</td>
</tr>
<tr>
<td></td>
<td>• &gt;x3 baseline</td>
</tr>
<tr>
<td></td>
<td>• sCr ≥4.0</td>
</tr>
<tr>
<td></td>
<td>• Dialysis</td>
</tr>
<tr>
<td><strong>Progression</strong></td>
<td>Progression to an upper stage of AKI or need for dialysis</td>
</tr>
<tr>
<td><strong>Regression</strong></td>
<td>Regression to a lower stage of AKI</td>
</tr>
<tr>
<td><strong>Response</strong></td>
<td>Null sCr does not improve</td>
</tr>
<tr>
<td></td>
<td>Partial</td>
</tr>
<tr>
<td></td>
<td>• sCr is reduced but ≥0.3 from baseline</td>
</tr>
<tr>
<td></td>
<td>Complete</td>
</tr>
<tr>
<td></td>
<td>• Return of sCr ≤0.3 from baseline</td>
</tr>
</tbody>
</table>

*^sCr obtained up to 3 months before AKI admission could be used instead*
HRS Definition: ICA 2015

- Flaws in the definition
  - Urinary output not carried over from KDIGO
  - Liver-MICU (n=3458) → AKI increased 1.4-fold adding UO
HRS Definition: ICA 2015

- New criteria for HRS (ICA 2015)

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<tr>
<td>Cirrhosis with ascites</td>
</tr>
<tr>
<td>Acute kidney injury according to AKI-ICA criteria</td>
</tr>
<tr>
<td>No response after 2 days without diuretics volume expansion with albumin (1 g/kg/d – maximum of 100 g/d)</td>
</tr>
<tr>
<td>Absence of shock</td>
</tr>
<tr>
<td>No recent use of nephrotoxic agents (NSAIDs, aminoglycosides, iodinated IV contrast)</td>
</tr>
<tr>
<td>Absence of evident parenchymal kidney damage:</td>
</tr>
<tr>
<td>• Proteinuria (&gt;500 mg/d)</td>
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<tr>
<td>• Microhematuria (&gt;50 RBC/HPF)</td>
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<tr>
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HRS vs. other AKI: why telling them apart?

- HRS is the subgroup of AKI carrying the worst prognosis

Etiology of AKI predicts mortality independently from MELD

Martin-Llahi. Gastroenterology 2011;144:488
Treating HRS

- RCT, n=46 (1:1) to: terlipressin + albumin (TA) vs albumin (A)
  - Type 1 and Type 2 with a Cr >2 mg/dL (ICA 1996)
  - Terlipressin dose: 1 g q/4h for 3 days, then 2 g q/4h
  - Outcomes: response (Cr <1.5 or ↓50% but ≥1.5)
  - Response (TA vs A): 43% & 9%; SV: 27% & 19% (ns)
- RCT, n=112 (1:1) to: terlipressin + albumin (TA) vs placebo + albumin (PA)
  - Only Type 1 (ICA 1996)
  - Terlipressin dose: 1 g q/6h for 4 days, then 2 g q/6h
  - Outcomes: response (Cr ≤1.5 for 48 hrs + no HD, LT or death)
  - Response (TA vs PA): 25% & 13% (ns); 180-d SV:
    - Significant for HRS reversal: 34% vs 13% → with improved SV
    - 22% had cardiac/ischemic AEs
    - 14% had cardiac/ischemic AEs
Treating HRS

- REVERSE RCT, n=196 (1:1) to: terlipressin vs pbo (all albumin)
  - Outcome: Response (Cr <1.5 ≥48 h apart), or Cr ↓ 20%; 90-d SV
  - Response (TA vs PA): 43% & 28% (p<0.05); SV 91% & 68% (p<0.05)

Response predicts SV
Treating HRS

- REVERSE study (terlipressin vs pbo): subanalysis HRS + SIRS
  - SIRS ≥2 of 3 (WBC >12000 or <4000, HR >90, HCO₃ <21 mmol/L)
  - 196 patients, 30% (n=58) with SIRS
Treating HRS

- Use of other vasoconstrictors

Terlipressin \( \rightarrow \) Norepinephrine \( \rightarrow \) Midodrine Octreotide

Sanyal. Gastroenterology 2008;134:1360
Alessandria. J Hepatol 2007;47:499
Sharma Am J Gastroenterol 2008;103:1689
Cavallin AASLD 2011
Treating HRS

- Hepatorenal syndrome:
  - The key is to increase the MAP!

![Meta-analysis of 501 patients across 21 studies](image-url)

Clinical Case 3

- AKI of patient on PPI
- Nephrology says AIN
- Patient started on corticosteroids or rituxan
- Patient with infectious complication
Issues to Discuss from Case 3

- Presumable frequency of AIN in cirrhosis
- Possibility of kidney biopsy – no transjugular
- High risks for infections in this population
AKI Etiology in Cirrhosis

Pre-Renal (Hypovolemia)
- Diuretics / Laxatives
- GI bleeding
- Cardiorenal

Post-Renal (Obstructive)
- Nephrolithiasis
- BPH
- Urothelial tumor

Renal (Parenchymal)
- ATN (ischemic, drugs)
- AIN
- GN (cryoglobulinemia)
- HRS
- Sepsis / Inflammation
- IgA nephropathy
- Bile cast nephropathy
- T2DM / Hypertension
- Other (disease specific)

<1%

60-70%

Parenchymal AKI in Cirrhosis

- Mostly unexplored
  - Clear lack of collaboration between specialists

Many patients had two or more cofactors of AKI

Nephrotoxics: NSAIDS, antibiotics, β-blockers, vasodilators (ACEi/ARB), iodinated contrast

Bucsics. Liver Int 2016;36:1649
Martin-Llahi. Gastroenterology 2011;140:488
Some Specific Causes of AKI in Cirrhosis

- NSAIDs
  - 30 patients among 780 in prospective database
  - 11 had persistent AKI

Similar to HRS / ATN

Similar to hypovolemic

Transient AKI

Persistent AKI

Elia. J Hepatol 2015;63:593
Some Specific Causes of AKI in Cirrhosis

- Iodinated contrast agents
  - Initial studies with no increased risk in cirrhosis

Contrast, ♂, ↓ Cr associated to AKI

♀, ascites, ↑ BUN

Very high risk in alcoholic hepatitis!
Some Specific Causes of AKI in Cirrhosis

• Acute interstitial nephritis (AIN)
  – Non-cirrhotic (biopsy-proven)
    • 15-30% de AKI (biopsy-proven) in the non-cirrhotic
    • 60-90% drug-induced: antibiotics, furosemide, NSAIDS (PPI’s 14%)

<table>
<thead>
<tr>
<th>n=100 AKI</th>
<th>n=30 Renal</th>
<th>n=9 AIN</th>
<th>n=7 Drugs</th>
<th>n=1 PPI</th>
</tr>
</thead>
</table>

• HCV & direct-acting antivirals (UAMS and U. Toronto)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>All - OR (95%CI)</th>
<th>p</th>
<th>SOF - OR (95%CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascites</td>
<td>4.69 (2.10-10.45)</td>
<td>&lt;0.001</td>
<td>4.44 (1.46-13.54)</td>
<td>0.009</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.96 (1.58-5.55)</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAID use</td>
<td>2.69 (1.08-6.72)</td>
<td>0.034</td>
<td>4.47 (1.32-15.19)</td>
<td>0.016</td>
</tr>
<tr>
<td>SOF vs. PI</td>
<td>0.40 (0.22-0.74)</td>
<td>0.004</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>
Un-precipitated AKI in Cirrhosis

- Satavaptan RCT-nested cohort study (D0-D7)
  - 1115 patients with no AKI precipitating events

<table>
<thead>
<tr>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>(≤1 LVP in prior 6 mo)</td>
<td>(LVP as needed)</td>
<td>(Refractory Ascites)</td>
</tr>
<tr>
<td>≤7 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4/434 (0.9%)</td>
<td>7/451 (1.6%)</td>
<td>9/230 (3.9%)</td>
</tr>
</tbody>
</table>

Stable/Pbo
≤55 weeks
(n=280)

- 1-year cumulative risk of 32%
  (70 AKI episodes in 165 patient-years)
  Risk was almost 6-fold in Group C compared to A

"AKI occurs in decompensated cirrhosis for the simple reason that inflammation is present (1.8% per 1-week)"

However, we should not push them towards AKI...
One diagnosis does not exclude another!

- ATN is more prevalent than what we think
  - 25 patients underwent kidney biopsy during LT at MCR

Not enough tissue

Cr ≥1.5 mg/dL
Acute tubular necrosis
HRS before LT
Nephrosclerosis

One diagnosis does not exclude another!
Conclusions

• “The unbearable lightness of kidney” in cirrhosis
  – Kidney failure is a must in decompensated cirrhosis
  – The issue is when it will occur and how to prevent it

• Need to follow the new definition of AKI and HRS

• Intravascular effective volume and renal vasoconstriction
  – NSAIDs, radiocontrast ACEi/ARB, nitrates, prazosin, etc.

• Always treat initially as prerenal
  – Stop diuretics/vasodilators & start albumin infusion
  – Consider alternative causes → good internal medicine!

• Start vasopressors early after a lack of response
  – Increase MAP by 5-10 mmHg
**AKI Algorithm**

**AKI – Stage 1**
- Eliminate risk factor (nephrotoxics, vasodilatadors)
- Treat conditions ↑ risk
- Expand volume (if indicated)

- **Resolves**
- **Stable**
- **Progresses**

**Close Follow Up**

- Decide according to context (i.e. sCr>1.5 mg/dL)

**How to adjust vasopressors and volume expanders:**
- **CVP:** >15 → albumina 25 mg/d; >18 → stop albumina + furosemide IV boluses
- **MAP:** ↑ <10 mmHg or **UO:** <200 mL (4 h): ↑ NE; Cr ↓ <25% (72 h): ↑ NE/midodrine

**AKI – Stages 2 y 3**
- Albumin 1 g/kg/d for 2 days (≤100 g/d)

- Test: U sediment, NaU, proteinuria, renal US, Foley, CVP, SAlb c/48 hrs

**Response**

- **Yes**
- **No**

**HRS criteria?**

- **Yes**
- **No**

- **Treat specific cause**

- **Terlipressin** 1-2 mg IV c/6 h
- **Midodrine** 7.5 mg tid (↑ 15 tid) + octreotide 100 mcg tid + albumina (25-50 g/d)
Thanks... Questions?